

Physics and the Quality of Life

THE American Physical Society has been provided with a fruitful talking point for its Washington meeting on April 24. Earlier in the year, Dr Robert H. March of the University of Wisconsin, with the support of the statutory number of members required to force consideration of the constitution of the society, put forward a constitutional amendment that would require the society not merely to encourage the advancement of physics and the diffusion of knowledge in physics, but so to organize its activities as to "increase man's understanding of nature and to contribute to the enhancement of the quality of life for all people". The proposed change in the rules would also require the society to "shun all those activities which are judged to contribute harmfully to the welfare of mankind". It remains to be seen what will emerge from the debate on the proposal which has been arranged for later this month, but the occasion could be interesting, especially if those who talk are able to avoid some of the obvious pitfalls, and if they can seriously address the question of whether and how learned societies—among which the American Physical Society is one of the most distinguished—can set out deliberately to direct their activities towards social goals.

The notion that learned societies should be concerned to "increase man's understanding of nature" is not of course a novelty. The full title of the Royal Society, after all, is "The Royal Society of London for Improving Natural Knowledge". Nobody will protest if the American Physical Society now formalizes its adherence to this old view. One question which should arise in Washington later this month, however, is whether the improvement of natural knowledge is by itself a contribution to the enhancement of the quality of life and whether a learned society as such is properly equipped to be more than a source of enlightenment. Much depends on the view taken of the relationship between scientific understanding and the social changes, benefits or otherwise, which may flow from it, and this is not a question in science but in sociology.

There are the strongest reasons for believing that scientific understanding is always socially beneficial. Although the immediate social consequences of the invention of gunpowder, for example, may have been unfortunate, who will now think that it would be possible for mankind to go about its business without being able to use explosives for extracting ores from the ground or for constructing dams or even the foundations of buildings? To be sure, the invention of explosives has also created awkward social problems—the need to control the use of firearms and so to regulate society that people are not tempted to use gelignite for political purposes. Much the same sequence of events has followed the exploitation of nuclear fission in the past few decades—nuclear weapons have been an unwelcome addition to the military arsenals and have forced on governments the need for greater restraint in international affairs, but uranium has quickly become an indispensable fuel, without which the

prospect of increasing scarcity of petroleum a century from now would be horrendous. And in many other fields of scientific research, the improvement of natural knowledge has been either directly beneficial—seventeenth century astronomy made navigation possible, for example—or has served to widen the options which are available to civilized societies. In short, there is a good deal to be said for the classical view that understanding of the natural world is always beneficial, at least in the long run. Certainly those who wish to argue otherwise must shoulder the burden of proof.

Does it follow from this that learned societies have done all that can reasonably be expected when they have done their best to foster the progress of research? This is where the argument becomes more interesting. It is only fair to say that many learned societies have vigorously and constructively involved themselves in public affairs. National academies have in many countries helped to set public education on desirable—and egalitarian—courses, for example. Others have helped to sharpen social problems as diverse as the hazards to human health from the smoking of cigarettes and the need that psychiatric questions should be considered as a part of public health. In Britain, the engineering institutions have a long record of constructive work in the improvement of the built environment. In the nature of things, however, it is hard for clubs of people united chiefly by this interest in some part of science to do much more than draw attention to social problems which they are especially fitted

NATURE/RI Conference on the Environment

The programme for the conference on Friday, April 28, has now been settled as follows:

Session 1 (1.45 p.m.)

Chairman: Professor Sir George Porter (Director, Royal Institution)

Speakers: Dr William Brass (London School of Hygiene and Tropical Medicine)—*Population*

Dr K. C. Dunham (Director, Institute of Geological Sciences)—*Resources of Fuels and Metals*

Dr Kenneth Mellanby (Director, Monks Wood Experimental Station)—*Pesticides and Pollution*

Mr J. S. Sawyer (Director of Research, Meteorological Office)—*The Carbon Dioxide Problem*

Session 2 (4.15 p.m.—5.45 p.m.)

Chairman: Mr John Maddox (Editor, *Nature*)
General Discussion

Applications for tickets are being dealt with on a first-come first-served basis



to define, but this, within reason, could well in present circumstances be regarded as an important part of their public function. If, for example, the American Physical Society and not the Chicago group of fission physicists had taken on the job of warning the American Government in 1945 of the potentially unexpected consequences of the use of nuclear weapons, that would have been creditable. In present circumstances, when people and even governments are increasingly anxious about the difficulties of foreseeing the consequences of scientific developments, it is right and proper that scientific societies should help out when they can.

But snags abound. The experience of the past shows clearly enough the dangers of dogmatism. For one thing, it is hard to be sure just what will be the potential benefits of new developments in science. The beneficial uses of high explosives would, for example, have been hard to predict at the end of the fifteenth century and, in the same spirit, there was a chance—slim though it always seemed—that the Plowshare programme for using nuclear explosives to make canals and harbours would have become a useful tool in modern society. It follows that societies embarking on a more constructive public function should go out of their way to limit public interventions to what they really know about. It would, for example, be proper for the American Physical Society to urge on the United States Administration the need for a better understanding of the chemical properties of the stratosphere before large numbers of supersonic transport aircraft come into service, but the society would run the risk of sacrificing its reputation and its potential influence if it were to come out at this stage against any serious programme for the development of supersonic transport aircraft. And now, of course, the environmental movement in the United States, even though a little below its zenith, provides too many seductive paths in which energy and reputation might be squandered.

The second important difficulty is that of knowing what constitutes the quality of life. Physicists, and scientists in general, must acknowledge that they are professionally out of their depth in this tortuous field. After all, it is not so long ago since the professions held to the view that economic growth as such must be a social benefit. Most probably they were right, for it is hard to see how daunting social problems will be solved unless countries of all kinds, rich and poor, are able to support not merely those who are employed in modern industry but the growing armies of the unemployed as well, not to mention the understaffed battalions needed to make society humane. Yet now there is, at least in the United States, growing support for the belief that economic growth is a snare and a delusion, and the risk of still further alienation between the well-to-do (from among whom the sceptics are largely recruited) and the poor (who still aspire to the old consumer durables of the 1930s). What position will the American Physical Society take on this important but enormously complicated issue? And what will it be able to say about the motor car, increasingly a public nuisance in metropolitan cities but still an essential ingredient of the libertarian way of life elsewhere? Will it take a view on the displacement of agricultural workers from the land which is prompted by increasing efficiency in agriculture, which adds to the pool of potentially unemployed in developing countries in particular but which may in the long run provide the means of important and desirable social change? Even those whose special

interests are the study of social transformations are chary of implying that they know for sure what constitutes the quality of life. It is hard to think that the American Physical Society is better qualified to make pronouncements on these matters. And the danger in naive assessments of the desirable characteristics of society is, of course, that attributes of the present or even the past are more cherished than potential attributes of the future.

What, then, are the ways in which the American Physical Society, and other learned societies, should seek to give expression to the sentiments which have inspired the proposed amendment to the constitution? The most constructive function properly within the competence of the society is to draw attention publicly to the ways in which research and development might contribute to the improvement of society or at least to the options which are available. The difficulty, as the activities of the White House and the National Science Foundation in recent months have shown clearly enough, is that it is easier to spend money on research that contributes to the solution of peripheral problems than to devise programmes which convincingly contribute to the central problems of modern society, poverty and injustice. Research on electrically driven motor vehicles, for example, may seem a virtuous contribution to the improvement of city life, but who is to say that it would not be better still to carry out the kind of analysis of transport networks within cities that might, after a long time and after massive reinvestment in housing and public transport, make it possible to dispense with independently driven vehicles altogether?

The most dangerous part of the proposed amendment to the constitution of the American Physical Society is that which would have it "shun those activities which are judged to contribute harmfully to the welfare of mankind". Not merely is there the difficulty of knowing for certain whether the most threatening aspects of research will in the long run turn out to be harmful, but it is unclear precisely how this part of the amended constitution would operate. Would there be an injunction against scientific conferences on proscribed topics, nuclear weapons, for example? Or would membership be denied to those who work in fields like this? And who in any case would judge what scientific activities are harmful? Learned societies have to their embarrassment acquired enough experience in the past few years to show how difficult it is to make corporate decisions about the desirability of particular apparently harmful activities. There are, for example, cogent reasons which persuade many scientists to the view that continued research on nuclear weapons or even chemical weapons is desirable, if only for defensive purposes. At the other extreme, there will be some who hold that large corporations are now such a menace that the research and development which they carry out is to be shunned. It is hard to see how a corporate view could be formed on matters like these without alienating at least a part of the membership. Is it sensible that a society whose reputation is founded on a common interest in physics should endanger its effectiveness by hoping to bring such thorny questions to a decision? It is, however, much easier to see how those among the members who hold strong views on particular subjects, even as minorities, might persuade their fellow members that it would be a public service to make public their anxieties, not so much as authoritative opinions of

the society at large but within its framework. In short, the demand that the American Physical Society should shun undesirable activities is unrealistic, but it could usefully provide a forum for discussion of issues like these.

Lord Rank's Legacy

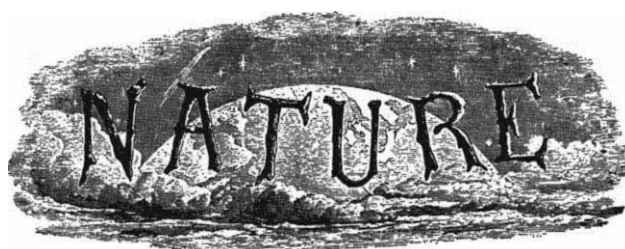
THE Nobel Foundation has done wonders, in the past half century, in providing a modern substitute for the old system by means of which monarchs would reward distinguished scientists with pensions enabling them to continue their work or to live above the poverty line in old age. On the whole, most Nobel prize winners have been eminently deserving of the honour and the reward, with the result that the institution of Nobel prizes has been a useful extra spur to competitiveness. To be sure, there have also been some less desirable consequences. The fact is that the Nobel Foundation's choices are almost inevitably less catholic than they might be. If most prize winners are deserving, not all deserving scientists seem to catch the eyes of the selection committees. It is, after all, a long time since an astronomer was awarded a Nobel prize (although Professor H. Alfvén's prize in 1970 was in part a recognition that some of his distinguished work has contributed in important ways to astrophysics and cosmology). So far, no radio astronomer has been honoured, although Professor C. H. Townes has turned to radio astronomy since his prize was awarded in 1964. Nor has there been, as yet, a recognition of the way in which geophysics has been transformed by those who have contributed to what is now the theory of plate tectonics. The result is that in spite of the diligence with which the Nobel committees set about their work, the results appear arbitrary in many ways. To complain at this may seem churlish, but it is clear that a scientist on whom the Nobel accolade has not fallen need not be ashamed to look his colleagues in the eye.

In circumstances like these, it is understandable that several charitable organizations should have sought to supplement what the Nobel Foundation does by setting up prize funds in special fields. In the United States, there are now handsome prizes for those who distinguish themselves in nuclear energy. Other foundations have tried to provide handsome prizes for engineers and technologists, consistently undervalued by the Nobel committees. The most recent step in this direction has been the generous bequest by the late Lord Rank which will provide a prize fund for those who work in human nutrition and in what is called optical electronics. By all accounts, the precise way in which the Rank fund will operate remains to be decided by the trustees and the two advisory committees. At current interest rates, there may be as much as £100,000 to spend each year. One of the most important decisions to be made is how much of the available income will be spent on prizes and how much will go on scholarships and fellowships. The first thing to be said is that human nutrition has not been entirely neglected by the Nobel Foundation, for Dr Norman Borlaug was awarded a Nobel prize in 1970 (admittedly for peace and not for science) for his work on the breeding of new strains of wheat and rice. The second is that the fields which have been chosen are so comparatively narrow that it will be hard

for the selection committees to find prize winners of a distinction comparable with that of most Nobel prize winners in each year of the operation of the fund. This is why it is to be hoped that the fund will concentrate chiefly on fellowships and other more familiar methods of encouraging worthwhile research. If there are to be prizes, they should be few and far between.

The question remains whether scientists in any discipline should be the sole recipients of the money which the committees hand out. After all, the sums involved are often so large that the unavoidable arbitrariness of the prize-giving process must necessarily be a cause of discontent among close colleagues. Moreover, the recipients of large money prizes are often the first people to acknowledge that their success in research is in part at least dependent on their colleagues and on the institutions in which they work. So is there not a case for asking that if the new Rank fund decides that money prizes should be an important part of its expenditure, these should be given not to deserving people but to the institutions at which they work? And is there not a case for asking that the Nobel Foundation itself should follow suit?

100 Years Ago



Error in Humboldt's Cosmos

I BEG to call the attention of geometers to what appears to me to be an inaccuracy in a work, which is, perhaps, the last which one would suspect to be capable of error—the "Cosmos" of Humboldt.

In vol. i. p. 293, he says, "I have found by a laborious investigation, which, from its nature, can only give a maximum limit, that the centre of gravity of the land at present above the level of the ocean is, in Europe, 630; in N. America, 702; in Asia, 1,062; and in S. America, 1,080 French feet (or 671, 748, 1,132, and 1,151 English feet) above the level of the sea." Sir John Herschel in his "Physical Geography" (Encyclop. Britt.) quotes these numbers of Humboldt as giving the height of the centre of gravity of these continents; and adds, "whence it follows, that the mean elevation of their surfaces (the doubles of these) are respectively 1,342, 1,496, 2,264, and 2,302." Herschel's conclusion is, of course, just, if Humboldt meant what he seems to say. But at the risk of being thought most presumptuous, I submit that Humboldt meant the height of the centre of gravity of the surface of the land; in other words, the mean height of the land; and by thus misleading Sir John Herschel he has by a *coup de plume* doubled all our continents.

I conclude, therefore, with the greatest deference, that Humboldt's "centre de gravité du volume" is an inaccurate expression, and that he meant "centre de gravité de la surface," or mean height. If this be so, Sir John Herschel has been led into the error of doubling our continents, which he estimates at a mean elevation of 1,800 feet.

It is a matter of some importance; for Sir Charles Lyell computes that the continent of N. America will be utterly washed away into the ocean by the ordinary processes of degradation in four and a half millions of years. If, indeed, this period is to be doubled, we can take a more cheerful view of the future of that continent. But I greatly fear with Sir Charles that it is limited to four and a half millions of years, unless some upheaval of the land shall protect its short span of existence.

JOHN CARRICK MOORE

113, Eaton Square, March 28

From Nature, 5, 479, April 18, 1872.

OLD WORLD

Stockholm Ahead

THE Royal Geographical Society was given this week a glimpse of the arguments which are likely to occupy the United Nations Conference on the Human Environment in Stockholm in June. At a symposium on the theme "Human Environment—The Impending Crisis", Mr Maurice Strong, Secretary General of the conference, who flattered his audience by commending the success of British measures against pollution and "the beauty of the English countryside", steered a careful line between doomsday and optimism. Warnings of disaster, he said, would at least help people to tackle urgent problems but "we cannot afford a sense of panic—once panic takes hold there is no hope for us. . . . It is as wrong to ignore the predictions of the doomsdayers as to think that what they prophesy is inevitable."

Mr Strong was optimistic about the outcome of the conference and pleased to be able to report agreement in the preparatory committees about the draft of a declaration to be adopted at the Stockholm conference. He was depressed at the prospect that the Soviet Union and other countries in Eastern Europe might not attend if the difficulty over the representation of East Germany was not settled in advance, but at the same time convinced that the problems of the environment were inescapably political, and he hoped that the Stockholm conference would produce "a new sense of direction for mankind" and a recognition that physical dependence on the environment entails international interdependence at a political level. He hoped that the action plan to be discussed at Stockholm would produce not merely a monitoring (Earthwatch) programme but also practical recommendations on environmental management and that the conference would agree to recommend to the General Assembly of the United Nations that there should be a special fund to finance a continuing programme including such things as an international system of a hundred stations for measuring air pollution, a ten-year moratorium on the hunting of the whale and schemes for the conservation of important plants.

The character of the British contribution to Stockholm was outlined by Mr Ralph Verney, who is the chairman of one of the four panels set up by the Secretary of State for the Environment to produce working documents for Stockholm. His own committee's re-

port, which Mr Verney says is unanimous, concludes that the rate of consumption of natural resources "puts the future of mankind at risk", and that, in Britain, there is too much mismanagement and waste. His working party is sceptical of nuclear energy and of economic growth.

Mr Neil Iliff, a member of the Royal Commission on Pollution and of the working party on pollution, was less sure that the British contribution to Stockholm would be clear cut and unambiguous. He was impressed with the diversity of views with which his committee had been presented and with the comparative ease and cheapness of measures to improve the environment already undertaken in Britain.

Professor T. R. E. Southwood of Imperial College, London, considered population growth to be the most serious worry and complained at leading articles in *Nature* on the subject. Professor Keith Clayton of the University of East Anglia took an opposing line, pointing out that discussions of resource scarcity usually ignore the effect of price increases and that the calculations sponsored by the Club of Rome are over-simple. He twitted Mr Strong with having failed to persuade developing countries to agree that population should be on the Stockholm agenda. "Why cannot the doomsday people recognize that they are sowing the seeds of their own doomsday by exaggeration?"

ASTRONOMY

Politics and Science

A CONFLICT between the Federal German Government and the Max Planck Society has developed over the proposed siting of the society's southern hemisphere observatory in South West Africa. The Federal German Government, although not a member of the United Nations, is rigorously keeping to the letter of the UN resolution that restricts investment in South Africa.

The Max Planck Society has responded strongly to the threatened withdrawal of funds by pointing out that tests carried out at several locations in the southern hemisphere have shown that the visibility in their chosen site in South West Africa is equally good as if not better than in other sites—including Chile, which has recently become a mecca for optical astronomers. And of prime importance, the cost of setting up an observatory in South West Africa will be the lowest of all the other suggested sites in the southern hemisphere—Chile, Argentina and Australia—no doubt helped by it being the nearest to Europe.

The site that the German astronomers would like for their observatory is in Namibia where a tract of desert land, near the South West African capital, Windhuk, has already been bought for DM12,000 (£1,200).

The overall plan for German astronomy includes the establishment of both a northern and southern hemisphere observatory. The northern hemisphere observatory has already been sited at Almeria in Spain, and one of the concerns of the German astronomers at present is where to site

the 3.5 m telescope which they have already ordered. According to the Max Planck Society, the decision on whether it is to be placed in the southern or northern hemisphere will depend on other European telescope projects—in particular the Germans will be interested in knowing the site for the proposed British northern hemisphere observatory. At present the British Science Research Council is sponsoring site tests in southern Italy and in the Canary Islands (Tenerife in the Canary Islands is known to be a good site for infrared and millimetre wavelength astronomy, which may also be included in the activities of the northern hemisphere observatory), and discussions are going on with the Spaniards over the possibility of obtaining a site in the Sierra Nevada mountains of Spain. When a decision is finally reached it is probable that a 150-inch telescope will be installed of similar size to that ordered by the Germans. But the progress on the reorganization of British astronomy which was to go with the establishment of a new observatory in the Mediterranean area is now said to be stagnant.

It seems likely that the objections of the Max Planck Society will not go beyond a verbal protest at this stage. In a statement issued recently the society points out that "the senate of the Max Planck Society will cooperate with the representatives of the federal government and give full consideration to political factors". A spokesman for the Federal Government said that if the society did carry on with its plans to build the observatory at Namibia then the treasury would cut off its finance for single projects. Last year this amounted to DM300 million.

Mr Peter Walker, Secretary of State for the Environment, said that the reports of the four working parties would be available at the end of April. He argued that those who complain that motor cars in the Lake District are a public nuisance should also recognize that they allow people to escape from the back streets of Sheffield and Stoke-on-Trent. It is, he said, "a question of balance" but he was dismayed at the difficulty of arranging for effective international institutions. He reminded his audience how quickly an awareness of environmental problems had spread and said that the recent argument about planning consent for electricity pylons near Hadrian's Wall would not have happened even a decade ago "and just think what trouble there would have been if I had been asked by the Ministry of Defence for planning permission to build a wall along the northern boundary between England and Scotland".

UNIVERSITIES

Engineering & Education

BRITAIN's education system suffers more from built-in inflexibility than any other in the world, according to Mr A. D. C. Peterson, Director of Educational Studies, University of Oxford. The chief defects are too much specialization at an early age and a false idea of the purpose of education; sixth formers should be taught to solve problems and to think—not to be the scholars that most of them will not, and do not wish, to be. To combat this inflexibility, Mr Peterson said that he hoped to introduce a combined engineering and education course at Oxford with the aim of producing good generalists for industry as well as teachers capable of approaching education in the way Mr Peterson advocates.

Mr Peterson was speaking on the first day of a three day conference on Technology and University Entrance, held at the University of Warwick last week, which met to discuss the problems of introducing new subjects such as engineering science into the sixth form, and of introducing joint honours courses into universities.

Mr B. G. H. Rowley of the University of Manchester Appointments Board also argued for greater flexibility—pointing out that 85 per cent of degree courses are single subject and only 15 per cent are general courses, while, of the jobs available to graduates, 70 per cent are of a general nature and only 30 per cent require specialized degrees. With the limit to the growth of traditional graduate jobs reached, graduates are having increasingly to take jobs unrelated to their degrees. In 1963

only 7 per cent of first degree chemistry graduates from the University of Manchester took jobs unrelated to their degree; last year that figure rose to 30 per cent. Figures like these argue for greater flexibility, Mr Rowley said, but they do not argue for curtailing higher education. The belief, subscribed to in the Robbins report of 1963, that more higher education means more economic growth is false, said Mr Rowley, and tying the growth of higher education to the economy by demand planning must be rejected.

But if flexible joint honours courses are necessary, where are they to be found? Mr D. Hutchings, of the Department of Educational Studies, University of Oxford, said that, in spite of the plans at Oxford to introduce an engineering science and education course, he thought that new courses would have to come from the polytechnics and newer universities, rather than from the older ones with their entrenched and independent science departments. Universities must not fall into the trap of producing mixed courses rather than interdisciplinary ones.

GOVERNMENT RESHUFFLE

They All Rolled Over...

AND five fell out, although life at the top remained virtually unaltered. Mr Heath's much anticipated ministerial reshuffle last week, in which five ministers were sacked and eleven backbenchers promoted, left the Departments of Health and Social Security, Education, and Defence and the Foreign Office unscathed, but produced several changes in the lower ranks of other departments that could affect those working in the fields of science and technology and industrial research and development.

The much criticized mammoth of the Heath government, the Department of Trade and Industry, suffers most from Mr Heath's axe, five of its six junior ministers losing their jobs or changing them. Sir John Eden, possibly the most criticized of the department's junior ministers, is moved out to become Minister of Posts and Telecommunications in place of Mr Christopher Chataway, who becomes Minister of Industrial Development, a new post in the DTI. Sir John's appointment will not please his critics with the already controversial question of the possible restructuring of broadcasting in 1976 coming up for consideration, when both the BBC charter and the ITV contracts are due to be reviewed. The appointment of the 41-year-old Mr Chataway will, however, be a popular one as he has no allegiance to the "lame ducks"

policy which has led Mr John Davies and the DTI into such troubled waters. Mr Anthony Grant, the only junior minister apart from Mr Michael Noble who has been at the DTI and survived, moves from being under-secretary for trade to be Mr Chataway's helper.

Mr Frederick Corfield and Mr David Price, minister and under-secretary for aerospace respectively, are two of the five ministers sacked by the Prime Minister. Although Mr Corfield's stock with the aerospace companies has risen steadily since he took office, there have been rumours that his future at DTI was in doubt ever since the Rolls-Royce fiasco—which apparently surprised him as much as everybody else last summer. Mr David Heseltine, the 39-year-old smooth-talking, long-haired under-secretary from the Department of the Environment, who was Conservative spokesman for transport when the party was in opposition, takes his place, aided by Mr Cranley Onslow as under-secretary, who has made himself a reputation as something of an expert on civil and military aircraft matters since he entered the Commons. With Concorde's sales yet to take off, Rolls-Royce (1971)'s future still in the gift of Lockheed's TriStar and the question of what to do after Concorde still to be decided, that expertise will be well tested.

Mr Nicholas Ridley, under-secretary for industry until last Friday, is also axed. Metrication and small firms figured among his brief and his place is being taken by Mr Peter Emery, a director of the North Sea oil and gas company Phillips Petroleum, with Mr Tom Boardman replacing Sir John Eden as minister for industry.

At the Ministry of Agriculture, Fisheries and Food Mr Anthony Stodart is promoted from parliamentary secretary to Minister of State and Mr Peter Mills, a farmer and chairman of the Conservative Agriculture Committee, takes his place, thus strengthening the ministry for the impending problems of Common Market entry.

The overall effect of Mr Heath's changes—there were twenty-nine changes in all—is to strengthen the government by the promotion of potential high flyers like Mr Chataway and Mr David Heseltine, while leaving himself free to make changes at the top possibly later this year, should the need arise. By next year, with Common Market entry presumably completed, Mr Geoffrey Rippon will be looking for a new job, while Sir Keith Joseph, Mr Anthony Barber and Mrs Margaret Thatcher, who survived this reshuffle in spite of some of the most virulent criticism any education minister has faced, may well be looking for new pastures.

NEW WORLD

Methadone Approval Sparks Controversies

by our Washington Correspondent

THE Food and Drug Administration (FDA) announced last week that it has found methadone to be a safe and effective drug for use in treating and rehabilitating heroin addicts, and that it will take the drug off its present investigational status. A clear victory for proponents of methadone maintenance? Not quite.

What has been decided is that methadone should be more readily available for approved treatment programmes, and to that end the FDA is conducting a survey to determine which programmes can be expanded with federal funds and where new ones are needed, but at the same time the FDA is proposing that the drug should be taken out of the hands of all physicians not attached to approved maintenance programmes. This will place methadone in a class of its own between investigational and approved new drug status. In effect, the FDA is trying, for the first time, to stop some physicians from prescribing a drug classed as safe and effective. Although the FDA can back up its case with some strong arguments, the precedent is unlikely to go unnoticed by the medical profession, and the announcement is also likely to open up some long standing controversies about the value of methadone for rehabilitating heroin addicts.

The new regulations, which are due to come into effect in 90 days, would remove methadone from all pharmacies so that hospitals and maintenance programmes would obtain their supplies directly from manufacturers. Physicians would no longer be able to prescribe the drug as a pain killer or as a cough medicine, except in rare cases in hospitals, and they would also no longer be able to give methadone to heroin addicts for detoxification. At present, physicians who are not attached to approved drug addiction clinics can prescribe methadone to addicts on a short term basis, but they must refer patients to the clinics for longer term treatment and rehabilitation.

Why has the FDA chosen to take the seemingly paradoxical step of declaring a drug safe and effective but slapping more controls on its use? The answer is relatively simple—to stamp out the flourishing black market in methadone. Overprescribing by physicians and by badly organized methadone clinics has made the drug relatively easy to come by, and there are many reports that it

is being sold on the streets to help heroin addicts tide themselves over when supplies of heroin itself are short. By channelling the drug solely through approved clinics, the FDA is hoping that it can dry up most of the black market sources of methadone and, from the other end of the process, by making more methadone clinics available to those addicts seeking treatment, one of the incentives for street sales will be reduced. As Dr Vincent Dole, who pioneered methadone maintenance in New York in 1965 suggested last week, "if all the addicts who want methadone were able to get into a programme, there would be no black market".

The FDA has also been forced into taking the decision on methadone by a variety of other factors, ranging from political and public pressure to do something to curb the rapidly increasing numbers of heroin addicts, to the FDA's failure to abide by its own regulations for drugs under investigation. The first step towards changing the status of methadone came last June when President Nixon launched the Administration's war against heroin addiction in a message to Congress. He stated then that he would soon seek to broaden the use of methadone in maintenance programmes, and eleven days later the Eli Lilly Company, the chief manufacturer of methadone in the United States, filed an application with the FDA to have the drug placed on an approved status. Then, in November last year, Dr Charles C. Edwards, Commissioner of the Food and Drug Administration, Dr John E. Ingersoll, Director of the Bureau of Narcotics and Dangerous Drugs and Dr Jerome Jaffe, Director of the Special Action Office for Drug Abuse Prevention, told the House Subcommittee on Public Health and Environment that methadone's investigational status would soon be lifted.

Dr Jaffe told the committee that use of methadone for maintenance of heroin addicts had become so widespread that "it is difficult to refer to a procedure that is being used with 50,000 people as an investigation", and Dr Edwards admitted that use of the drug had far outgrown its status. "We have now reached the point where we must either approve the drug or revoke INDs (permits for clinical investigation) for the vast majority of the existing methadone treatment programmes and return to a handful of true research studies", Edwards told the committee.

To add to the problem, the FDA has

been under considerable pressure from the White House and from influential proponents of methadone maintenance to broaden the use of the drug. A member of the Special Action Office said last week, for example, that if it had not been for considerable pressure applied by the office, the FDA might still be content to allow methadone's investigatory status to be stretched even further beyond the bounds of credibility. The political incentive for broadening the use of methadone lies in the fact that the Administration's attempts to combat heroin addiction are likely to become a potent issue in the forthcoming election—a survey carried out for the National Commission on Marihuana and Drug Abuse, for example, placed drug addiction third in a list of issues about which the American public is most concerned (behind the economy and the war, but ahead of the environment). On a purely practical level, the FDA thus had no option but to lift the investigatory status of methadone.

But proponents of methadone treatment also claim that there are sound medical reasons for giving the drug an official stamp of approval. Dr Dole said in a telephone interview last week, for example, that the change of status is "overdue". "The true function of an IND is to govern safety and efficacy", Dr Dole pointed out and "the evidence to support methadone's safety and efficacy has long since been in". And Dr Dole's views were echoed many times at the Fourth National Conference on Methadone Treatment, held in San Francisco in January. Summing up the conference, Dr Avram Goldstein of Stanford University said "the investigational status of methadone is clearly at an end". The papers presented at the conference "leave little doubt that methadone is an effective tool in the management of narcotic addiction".

One aspect which has, however, clouded analyses of the efficacy of methadone in treatment of heroin addiction is the FDA's failure to monitor the investigation of the drug properly. Dr Edwards announced last week, for example, that the FDA is only now training staff to conduct a nation-wide survey of how well methadone clinics are working, and to find out how many addicts are receiving the drug. Preliminary results of the survey, he said, should be available in about 45 days. At least those results will become available before the proposed new

regulations on methadone come into effect, but such basic information on a drug under clinical investigation should be collected by the FDA on a continuing basis. Asked last week why this has not been done in the past, a spokesman for the agency pointed out that seven clinics have been shut down because they were not operating in accordance with the FDA's guidelines (there are now about 450 clinics in operation) and that the agency does not have the facilities to collect every detail on the programme. "Methadone is not the only IND we have", he said.

If the FDA's survey can provide an estimate of the number of addicts receiving methadone, at least that will be a welcome step. In June last year, at hearings before the House of Representatives Select Committee on Crime, FDA officials estimated that between 20,000 and 30,000 addicts were on methadone maintenance, but by the end of the year their estimates had doubled and last week Dr Edwards suggested that as many as 65,000 may be receiving the drug.

The medical controversies surrounding the use of methadone in treating heroin addicts centre chiefly on the fact that methadone itself is an addictive opiate. Essentially what a maintenance programme does is to substitute dependence on methadone for dependence on heroin, the value being that methadone is longer acting, it does not produce euphoria, it can be taken orally, and the addict can lead a relatively normal and productive life. Proponents of methadone maintenance argue that an addict can take methadone and lead a normal life in much the same way as a diabetic has to take insulin to keep going. For the addict, of course, methadone prevents the onset of withdrawal symptoms when he stops taking heroin and if the drug is taken in sufficiently high doses, it will block the euphoric effects of any heroin that he may also take.

But those who argue against the use of methadone in treating heroin addicts claim that it is chiefly a method for reducing addict-related crime, rather than for rehabilitating addicts. It is often claimed, for example, that it is more difficult to withdraw from methadone than from heroin, since withdrawal symptoms last for several weeks rather than for a few days (withdrawal symptoms are, however, usually less severe with methadone than with heroin), and many radical black groups are opposed to methadone maintenance because they see it as simply a means of keeping the black population (which makes up a disproportionate percentage of the addict population) subdued. Studies conducted by Dr Goldstein in California, have, however, shown that addicts can be taken off methadone

without suffering withdrawal symptoms if doses of the drug are reduced by less than 10 per cent a week—a process that takes several months.

What many opponents of methadone maintenance argue is that the treatment itself does not attack the underlying psychological factors that lead to addiction in the first place. But the point is accepted by most of those who use the technique. Dr Jaffe, for example, told the Fourth National Conference on Methadone Treatment, that methadone "is not a panacea", and at the same conference, virtually every speaker emphasized the fact that methadone should be only one tool in a treatment programme. Dr Goldstein suggested, for example, that it "is a fantastically effective tool for bringing addicts into a new and helpful kind of therapeutic environment". In short, addiction to methadone is more socially acceptable than addiction to heroin, it is less debilitating for the addict, but methadone itself is not the only answer to rehabilitating an addict.

One doubt that has been aired about methadone maintenance therapy centres around conflicting ideas about the physiological basis of drug addiction. Dr Dole has argued that addiction to opiates may cause a basic metabolic change that in turn causes drug hunger, and that methadone compensates for that change. But if that theory is correct, and if the metabolic change is reversible, giving an addict methadone over a long period of time may in fact prolong and aggravate the underlying physiological condition.

Although that argument is dismissed as a red herring by many, it does emphasize the fact that there is only an incomplete understanding of the pharmacological basis of addiction and of how methadone works. Essentially what happens when a person becomes addicted to heroin is that his tolerance to the drug is increased—it requires a higher than normal amount of opiate in his brain for him to feel the effects. If, however, the opiate in his brain declines below this increased tolerance level, withdrawal symptoms will eventually be precipitated. What methadone does is to maintain the level of opiates above the tolerance level, so that removal of heroin will not lead to withdrawal effects. In addition, because of the phenomenon of cross tolerance, administration of any other opiate in a dose which itself is not sufficient to reach the tolerance level, will not produce euphoria.

How these effects are interpreted at the molecular level is, however, an open question, although there is no shortage of theory. Among the theories that have been voiced are that opiates affect the catecholamine system by acting on both the receptors and the pre-

synaptic nerve endings in the brain. It has been suggested that heroin may attach itself to receptor sites, thereby blocking the access of neurotransmitters, and at the same time it may alter the characteristics of the receptor, making it more sensitive to the neurotransmitters. This theory suggests that withdrawal effects are produced when the narcotic block is removed and neurotransmitters reach the sensitized receptor, and that methadone maintains the block. Another suggestion is that the narcotic may act on the presynaptic nerve ending, by releasing stored neurotransmitters, blocking the reuptake of transmitters or by altering the enzyme that leads to the synthesis of the neurotransmitters. Both Dr Goldstein and Dr Dole emphasized last week that these suggestions have no practical confirmation at all. At least one effect of the present concern about drug addiction, however, is that funds for research into the biology and pharmacology of addiction should be more easy to come by—the drug abuse act setting up the Special Action Office for Drug Abuse Prevention, that was recently passed by Congress and signed into law by President Nixon, includes authorizations of \$75 million over the next three years for research into drug addiction.

So far, reaction to the FDA's announcement that it is taking methadone off its investigational status has been muted. But Paul G. Rogers, chairman of the House of Representatives Subcommittee on Public Health and Environment, was very sceptical in November when the FDA announced its intentions. Rogers then warned that removal of the drug from IND status would "be a disservice to the nation", and although he was briefed by the FDA before last week's announcement, an aide in his office said last week that there will probably be hearings by the subcommittee on the new regulations.

As for organized medicine, the American Medical Association has made no formal statement, but will probably not oppose the rationale behind the recommended regulations. A statement by the AMA's Council on Mental Health and Committee on Drug Dependence, published in the March 20 issue of the *Journal of the American Medical Association*, suggests that "methadone maintenance is not feasible in the usual office practice of private physicians. . . . The individual physician is also not in a position to assure against redistribution of the drug into illicit channels. . . ." But how the AMA and individual physicians will react to the federal government's attempt in effect to deprive them of the right to treat their patients with an approved drug and in the manner they think best, remains to be seen.

The Tutankhamun Exhibition

Dr I. E. S. Edwards, Keeper of Egyptian Antiquities at the British Museum, describes the sequence of events, including some strokes of luck, that has culminated in the Tutankhamun Exhibition at the British Museum.

THE Tutankhamun Exhibition at the British Museum represents the culmination of a modest plan conceived some ten years ago when the Arts Council accepted an offer from the Egyptian authorities to show in London a travelling exhibition of works of art dating from both Pharaonic and Islamic times. With a view to increasing the popular appeal of the exhibition, which had already been displayed in several European capitals, it was decided to ask the Cairo Museum to supplement it with a few relatively unimportant pieces from the tomb of Tutankhamun. We had, however, been unknowingly forestalled by a group of American museums, whose negotiations with the Egyptian authorities for a more ambitious exhibition than we had contemplated were well advanced and, although the Arts Council was offered the same exhibition on its way back from the United States, it was feared that two exhibitions of Egyptian art within so short a period of time would exceed the public demand. The plan was accordingly deferred, but not abandoned. It was next taken up five years later, in 1967, and for a time hopes were entertained that the objects shown in Paris would subsequently come to London. They were dashed, however, by the outbreak of the war between Israel and her Arab neighbours, just when it seemed likely that consent would be given. The present exhibition was agreed in principle in October 1968 and the objects were selected a year later. The previous exhibitions had shown that the delicate objects could be moved safely over long distances and be exposed to some inevitable climatic changes without damage, and the experience thus gained allowed the Egyptian authorities to agree to our request for fifty pieces, a much larger number than had been sent to America, Japan or France.

Under Amenophis III, who was either Tutankhamun's grandfather or his father, Egypt had attained its highest level of economic prosperity; gold was "as dust" and artists and craftsmen were among the beneficiaries from the boom. His tomb may well have been the richest of all, though there is no actual evidence to prove it. By the time of Tutankhamun the national wealth must have declined appreciably, but there was probably still enough gold available, as well as artistic and tech-

nical skill, to provide the king with personal and funerary possessions which were not greatly inferior to those of Amenophis III.

Its preservation was the result of several fortuitous events. Owing to his premature death, the tomb which was being constructed for him in the western branch of the valley could not be completed in time for his funeral and consequently a small tomb, which was probably intended for his elderly vizier and successor Ay, was hastily adapted for his use. Its entrance lay on the level floor of the valley and not in the walls of rock at the sides like the entrances of most of the other royal tombs. Thus placed, its mount was soon covered with wind-blown sand, and after the first heavy rainfall—usually only once in twelve to fifteen years—it would have been buried under a layer of mud, dried quickly by the sun, which would make it indistinguishable from the surrounding terrain.

It is true that robbers broke into the tomb, probably on two occasions, but their visits must have been brief. Given time, they would certainly have stripped it of all its precious objects. By chance, however, an official, who had a personal interest in its preservation, was working on another royal tomb nearby. His name was Maya, and in his official capacity as Superintendent of Building Works in the Necropolis he was almost certainly responsible for the construction of the tombs of Tutankhamun, Ay and Horemheb. When Tutankhamun's tomb was violated, the news would have reached Maya within a few hours and he would have been able not only to take immediate action to re-cover the entrance, but also to take steps to bring the thieves to book. Some of the objects which they had stolen were found in an underground chamber near the tomb in 1907 by Theodore Davis, an American archaeologist, which suggests that the robbers did not survive to get away with all they had removed. How long Maya remained in office is uncertain, but it was probably long enough for the exact location of the tomb to be forgotten. Some two hundred years later its existence was so completely unknown that Ramesses VI excavated his rock-tomb dangerously close to it and the men engaged on the work actually built their huts on top of the rock-cut staircase leading down

to Tutankhamun's tomb. They also dumped some of the rubble removed from the new tomb around the huts, thus unwittingly giving Tutankhamun's tomb further protection.

If the preservation of the tomb in antiquity owed much to a series of lucky chances, its discovery fifty years ago can be ascribed ultimately to a motor accident which undermined Lord Carnarvon's health so seriously that he went to Egypt in 1903 to escape the effects of a winter in England. Once there, he began to take an interest in Egyptian antiquities and works of art, even to the extent of embarking on his own excavations on the west bank of the river at Thebes in the year 1906. A year later he engaged Howard Carter to supervise the work.

At about the same time, Theodore Davis was excavating in the Valley of the Kings and had found a pit containing linen bandages, bags of natron, pottery wine-jars, floral collars and bones, the significance of which he failed to understand. It was Herbert Winlock, Curator of the Egyptian Department in the Metropolitan Museum, New York, who first realized their importance. On examining the linen he noticed that some of it bore the name of Tutankhamun written in ink and also the year of its manufacture. What Davis had found was in fact some of the material used by Tutankhamun's embalmers when they mummified his body and relics of the banquet attended by the chief mourners at his funeral. From the moment when Winlock made this discovery, it was certain that Tutankhamun had been buried in the valley, and probably not far from the pit in which the linen had been placed. What was not certain was that the tomb itself had survived in an identifiable condition. Theodore Davis relinquished his licence to excavate in the valley in 1914 and the concession was immediately granted to Lord Carnarvon. Both he and Howard Carter were well aware that their efforts might be fruitless, and nothing which came to light in the first six seasons gave them any encouragement to think otherwise. No organization dependent on public funds could possibly have continued the search for six seasons without result. Lord Carnarvon, however, retained his confidence in Howard Carter's judgment, though it was near to breaking-point by the end. Carter too was a man of exceptional determination and tenacity. Chance had played an important part in bringing them together and their collaboration ended triumphantly in the seventh season with the discovery of what was very probably one of the richest tombs of all time.

NEWS AND VIEWS

Prospects in Pre-Mesozoic Palaeomagnetism

THE article by Irving, Park and Roy, which appears on page 344 of this issue of *Nature*, and the one by Spall, which appeared two weeks ago (*Nature*, 236, 219; 1972), offer a welcome sign that palaeomagnetism is not only alive and well but is at last returning to what it can do best—the delineation of large-scale movements of continents or crustal plates over long periods of geological time.

Having triggered a conceptual revolution in the whole basis of the Earth sciences by offering, during the early to middle 1960s, the first convincing quantitative evidence that continental drift has been taking place over the past 200 million years, palaeomagnetism in the strict sense quickly moved out of the limelight to make way for sea floor spreading and plate tectonics which it begat. As a result, a fear arose in some quarters that the future of palaeomagnetism lay in its application to comparatively small-scale geological problems and perhaps even in a return to what it originally set out to do many decades ago—to describe the behaviour of the Earth's magnetic field over the period covered by the rock record. Such aims, of course, are far from unimportant; but there has nevertheless been a feeling in recent years that in the aftermath of revolution the euphoric days of palaeomagnetism are over.

Ironically, the success of the new global tectonics has tended to obscure the fact that the revolution in the Earth sciences has been based largely on a period of time which represents less than five per cent of the Earth's history. By contrast, the interval of time which elapsed between the formation of the world's oldest known continental rock and the onset of continental drift in the Wegenerian sense amounts to more than two-thirds of the age of the Earth, most of it lumped together in what is conveniently, though not very enlighteningly, called the Precambrian. In principle at least, therefore, there is scope here for a great deal of palaeomagnetic work of the most ambitious kind and an opportunity to extend the successes of the Mesozoic and Cainozoic into the Palaeozoic and beyond.

Palaeomagnetists must thus try to find out what was happening to the Earth's continents or crustal plates before the breakup of Laurasia and Gondwanaland. Was there a single continental mass which had existed in more or less the same form since the differentiation which produced it, or was Laurasia-Gondwanaland merely a temporary phenomenon—a chance coalescence of continental masses subject to continental or sporadic drift extending into the indefinite past?

There is now, of course, some geological evidence which would suggest that Laurasia-Gondwanaland was indeed the product of the coming together of continental masses previously in other configurations; though equally, there is other evidence which suggests just the opposite. Allowing for the uncertainties inherent in geological interpretations of this type, especially those relating to the dimmer geological past, it seems certain that the quantitative approach of palaeomagnetism will again be required to produce convincing evidence one way or another. (In

some senses the situation here is analogous to that which obtained before the palaeomagnetic "proof" of Wegenerian drift; but in the self-righteousness of hindsight some geologists will no doubt regard such an interpretation as unpardonable arrogance on the part of palaeomagnetists.)

It would perhaps be wise to recognize from the start that in seeking to extend the potential of palaeomagnetism back beyond the Mesozoic there will be additional problems not generally encountered in dealing with the past 200 million years. In the first instance, there is the simple question of accumulating enough data. Although a certain quantity of pre-Mesozoic palaeomagnetic data exists already, to extend the record back from 200 million years to even 2,000 million years (that is, by a factor of ten) in sufficient detail to enable acceptable conclusions to be drawn could involve anything up to a ten-fold increase in effort on simple arithmetic grounds alone; and yet there are few signs that more than a handful of people are willing to devote themselves to fitting small pieces of the vastly greater jigsaw. This assumes, of course, that there are sufficient rocks to be had in the first place. In practice, the completeness of the rock record decreases with increasing age; and it may never be possible to determine complete pole paths for all continents nor even, in many cases, to apply the usual consistency tests by comparing the palaeomagnetic results from widely separated rock units of the same age.

Moreover, how are continents or crustal plates to be defined in this context? It is one thing to take the present continents and fit them together in some ancient configuration; it is quite another to take that single ancient landmass, split it up into pieces of unknown shape, and plot the course of each piece, even supposing that suitable rocks were sufficiently plentiful. And even where suitable rocks exist, palaeomagnetic data may not be easily acquired. Experience shows that the older the rock the more difficult it is to obtain the ancient geomagnetic field direction and to assess the reliability of such a direction once obtained. Quite simply, the older a rock is, the longer it has been susceptible to the vagaries of the Earth's history and the greater the chance that its original magnetization may have been modified in some unknown, and possibly undetectable, way. Add to this the comparable difficulties in dating rocks with greater exposure to the processes of alteration, not to mention the large absolute errors inherent even in reliable ages (obviously, a ± 5 per cent error in a 2,000 million year old rock gives a total error spread equal to the whole period of Wegenerian drift), and the picture becomes pessimistic indeed.

Perhaps this view is over-pessimistic. In other words, perhaps it is quite wrong to judge the potential of pre-Mesozoic palaeomagnetism purely in the light of the magnificent successes relating to the past 200 million years. The truth is that the greater problems inherent in coming to terms with the longer period may preclude the achievement of even the degree of completeness already achieved for the Mesozoic-Cainozoic; but that is not to

say that significant advances may not be made by making a number of more limited, less ambitious assaults. Thus it may never be possible to compare the complete pre-Mesozoic polar wandering paths for several continental masses; but if it can be convincingly demonstrated that one or two pairs of such masses have moved relative to each other, albeit over limited intervals of time, the existence of some type of pre-Wegenerian drift will have been established—and that in itself will not have been an insignificant achievement.

Basically, this is the approach taken by both Spall and Irving *et al.* Thus Spall, although admitting the possibility of deficient data, has compared

the palaeomagnetic results from North America and southern Africa (the only two regions from which sufficient data of any quality are available) for the period 2,000–1,000 million years ago, and concludes tentatively that Precambrian drift did, in fact, occur. Likewise, Irving and his colleagues use palaeomagnetic data to show that the Grenville Province, which forms the younger, most south-westerly part of the Canadian Shield, was once displaced by several thousand kilometres with respect to the rest of the (older) Shield. Two swallows may not make a summer; but the evidence for pre-Mesozoic drift nevertheless begins to look more impressive as time goes by.—P. J. S.

Frame Shift Hot Spots

THE existence of the aptly named hot spots—regions in bacteriophage genes which mutate at very much higher frequencies than neighbouring regions of the same gene—was revealed as long ago as 1961 by Benzer during his classic analysis of the r_{II} A and r_{II} B cistrons of bacteriophage T4. As Benzer reported, the location of point mutations in the r_{II} region is very far from random; for example, of 1,612 spontaneous mutants mapping at 251 sites in this region, more than 500 mapped at a hot spot in the r_{II} B cistron and a further 300 mapped at a hot spot in the r_{II} A cistron, and, further, mutations induced by a variety of chemical mutagens were found not to cluster in these two spontaneous mutation hot spots.

Clearly, in at least some phage genes certain segments of DNA are more readily mutated than others, but clues to explain this have been very hard to come by and it is small exaggeration to say that for the past decade the molecular basis of the phenomenon of hot spots has remained almost totally obscure. The recent work of Streisinger and his colleagues on frame shift mutants of the lysozyme gene of phage T4 has, however, at last provided a chink of light. On page 338 of this issue of *Nature* Okada, Streisinger and their colleagues report a set of experiments which lead them to conclude that the high frequency of frame shift mutation and reverse mutation in the lysozyme gene may stem from the occurrence of sequences of five or more consecutive and identical base pairs.

The mutation they have chiefly worked with, $eJD11$, reverts to wild type at a frequency more than a hundred times greater than that of any other site in the lysozyme gene so far examined, and revertants “appeared identical to e^+ phage in every respect”. Furthermore, recombination tests proved that the reversion of the $eJD11$ mutation is a true reversion and does not result from the occurrence of a second compensatory mutation which might give rise to pseudowild type phage. And an accurate determination of the rate of reversion of the double mutant $eJD10$ - $eJD11$ to the single mutant $eJD10$ indicates that reversion frequency at the $eJD11$ site exceeds the summed total forward mutation frequency at all other sites in the gene. In short, the $eJD11$ mutation is very labile. But what is so special about the DNA at this site in the lysozyme gene?

In order to obtain information about the base sequence of the $eJD11$ site Okada, Streisinger and their colleagues analysed the amino-acid sequence of lysozyme specified by wild type e^+ phage, the double mutant $eJD10eJD11$ and that specified by a triple mutant designated $eJD10eJ17eJ42$ which is a pseudowild type. Their aim was to pin-point the changes in amino-acid sequence which result from these various mutations and by using accepted codon assignments thereby to arrive at the most probable base sequence of the $eJD11$ region. To cut a long and complex story short they were able to conclude, first, that although the $eJD10$ mutation consists of a single base deletion the $eJD11$

must consist of the addition of either an A or a G residue.

In the wild type lysozyme the amino-acids threonine, lysine and serine occur at the $eJD11$ site and there is good reason to believe that they are coded by the codons ACA, AAA, AGU, because fourteen of fifteen codons in the lysozyme gene have been identified in A or in U. Okada *et al.* favour therefore the idea that the mutation of e^+ wild type to $eJD11$ occurs when an additional A residue, rather than a G residue, is inserted in this sequence to give the sequence ACAAAAAGU with six instead of five consecutive A residues. Reversion of the $eJD11$ mutation would, of course, involve the deletion of the additional A residue and the restoration of the wild type sequence.

The striking feature of the base sequence of the wild type DNA at the $eJD11$ site is, of course, the presence of five consecutive A residues (AT base pairs in the double stranded DNA). Owen, one of the group, has apparently subsequently found that five other mutational sites in the lysozyme gene, all of which revert at unusually high frequencies, most probably also contain sequences of five identical base pairs.

It seems therefore that at least in this gene a high frequency of frame shift mutation and reversion (the insertion and deletion of a base pair) is associated with and perhaps caused by the presence of a sequence of consecutive identical base pairs in the wild type double stranded DNA. Whether, however, such runs of consecutive identical bases are associated with hot spots of the other class of mutations, which arise from the substitution of one base for another, rather than the deletion or insertion of a base, remains to be seen.—From our Cell Biology Correspondent.

PROTEINS

Energetic View

from our Molecular Biology Correspondent

THE appearance of yet another formulation for cooperative ligand binding by proteins may well cause many a reader to utter a cry of despair and turn to more congenial topics. But this is not merely another wrangle about concerted and sequential mechanisms, but an indictment of both as physically unrealistic and at times downright misleading. Weber (*Biochemistry*, 11, 864; 1972) has produced a counterblast to the tacitly accepted notions of linked

functions that in his view visit upon proteins the attributes of macroscopic contrivances, such as cuckoo clocks. He rejects the principle, implicit in all extant formulations of linked ligand binding equilibria, that the protein can assume only a small number of thermodynamically defined conformations, the equilibrium between which is controlled by environmental factors, in particular by the concentration of the ligands.

As a prototype Weber considers first a single chain with separate binding sites for two different species of ligand. If one defines three conformational states, one prevailing in the absence of ligand, another characterized by high affinity for the first ligand and a third by high affinity for the other ligand, then the addition of one or the other ligand will drive the conformation into one of the latter two states. What, however, if both ligands are present in large, saturating concentrations? Neither will be expected to displace the other; rather the protein will enter a new conformational state, structurally intermediate between the two singly liganded forms. This simple argument, says Weber, exposes the speciousness of schemes based on (in this system) three inherently permissible canonical conformational states.

Rather than attempt to fit observed binding curves with sets of apparent equilibrium constants between experimentally inaccessible hypothetical structures, Weber advocates a description simply in terms of free energies of the variously liganded states. The measured, or apparent, free energy of binding of the first ligand in the prototypic system will include the free energy of conformational adjustment of the protein. A similar quantity can be defined for the binding of the second ligand to the free protein. When both ligands are bound, however, the free energy change is different again: the increment between the apparent free energy of binding of both ligands, and the sum of the apparent free energies of binding of either ligand in the absence of the other, is referred to as the coupling free energy, and may be zero if the conformational effects of the ligands are confined to independent structural elements, negative if the two ligand species assist each other's binding and positive if they oppose it. The free energy of binding of a second ligand in the presence of saturating concentrations of the first is called the conditional free energy.

Weber enlarges on this general scheme by considering, first, the effect of a second or modifying ligand species on one that binds at more than one site, and, second, the binding of ligands to oligomeric proteins. It is a commonplace that the attachment of ligands will tend to change the strength of the association between subunits, and indeed

it is to be expected that any change within a polypeptide chain, occasioned by the binding of a ligand, will be transmitted to other parts of the molecule. The subunit interfaces are evidently most vulnerable to this kind of disturbance, for breakdown of quaternary structure invariably occurs much more readily than denaturation. Because one is concerned here with free energies not far removed from thermal energy, the most trifling distortions at atomic contact points may be involved. If the greater part of such a change is effected by the association of the first subunit with its ligand, the binding of the second ligand will be changed, and cooperativity will result.

Weber notes next that both the allosteric, or concerted interaction model, and the sequential formulation, are arbitrarily restricted versions of his more general scheme, whereby cooperativity (or anticooperativity) follows from the need to balance the free energy changes that define the variously liganded states. In order to extract relative ligand binding constants for a tetrameric species, such as haemoglobin, one requires a subunit interaction scheme. The parameters used can be converted into a Hill constant, which is the simplest measure of the cooperativity, and to obtain a value of the order found in haemoglobin, it must be assumed that a change in oxygenation state of one subunit affects its contacts with two neighbours.

Weber shows that for such a situation the progressive absorption of twofold intersubunit distortions as successive oxygens are bound leads on simply statistical grounds to a large value for the fourth affinity constant. Further, the consequences of binding of a single cofactor molecule (2,3-diphosphoglycerate) on the cooperativity and affinity of oxygen binding have been re-examined, and reveal what appear to be some loose conclusions in earlier thinking about such systems: the effects of oxygenation can be shown to depend critically on the cofactor concentration. In particular the simple free energy relations lead to rejection of the view that attainment of a unique oxyhaemoglobin conformation is linked to the release of cofactor on complete oxygenation.

It is clear, of course, that in many cases formulations involving a few rigidly defined conformational states will satisfy all observations. A good example, showing an excellent fit to oxygen and cofactor binding data for haemoglobin in terms of a two-state model, is given, for instance, by Ogata and McConnell (*Proc. US Nat. Acad. Sci.*, **69**, 335; 1972). Weber, however, would argue that such a fit may well be illusory, and involves the manipulation of physically unreal parameters.

At best, spectroscopic methods, such as are commonly used for following changes of conformation, observe only averages over populations of states indistinguishable by available procedures. His view that the kind of mechanical rigidity that Perutz's description of the oxygenation process imputes to haemoglobin is fundamentally unrealistic, and that there is no reason to suppose that different regions of a protein molecule may not be subject to quite independent conformational adjustment, will not be welcomed in all quarters.

Whatever one's prejudices on this issue, on the other hand, there can be no doubt that the free energy formulation of linked functions, as Weber expounds it, will commend itself to anybody looking for an intuitively satisfying and logically coherent description of even very complex systems. Its application does not necessarily predicate a choice between the two rather different concepts of protein conformation.

PREDATION

Surplus Killings

from our Animal Behaviour Correspondent

MANY carnivores have been reported to kill far more prey animals than they could possibly consume at the time. Such "surplus killings", for example, by a fox in a hen house, pose certain problems, because the predator would seem to be wasting energy and endangering its own food supply. H. Kruuk (*J. Zool.*, **166**, 233; 1972) draws together observations on various carnivores in which "massacres" of large numbers of prey have been reported and attempts to explain them.

One very interesting generalization which he is able to make is that such events seem especially likely to occur at times when the natural defences of the prey are reduced, that is, they form an easy kill. For example, surplus killings of gulls by foxes were found to occur particularly on dark nights when the gulls apparently put up no resistance. A large scale killing of Thomson's gazelles by spotted hyenas in the Serengeti National Park also occurred on a dark night, when Kruuk's analysis of tracks indicated that the hyenas had walked quietly from one victim to another and few signs of chase or struggle were apparent. These easy targets seemed to elicit killing even though the act of eating itself was inhibited.

One of the advantages to be gained from surplus killing may be that the carcass is available for food later on and indeed some species are known to make "larders" of stored food. But it



Surplus killings of gulls by foxes.

is not clear whether, on balance, surplus killing is a good thing or a bad thing for the animal doing it. In the case of the foxes killing gulls, Kruuk argues that it might in fact wipe out the whole population in a particular area, to the detriment of the foxes themselves. It is, however, a relatively rare phenomenon and may simply reflect upset of otherwise efficient hunting and killing behaviour.

SELENOLOGY

Surface Structure

from our Geomagnetism Correspondent

IN addition to the so-called Passive Seismic Experiment (PSE) instituted by earlier Apollo missions, the Apollo 14 astronauts took the first steps in carrying out an Active Seismic Experiment (ASE). The difference between the PSE and the ASE is simply that, whereas the first made use principally of natural sources such as meteorite impacts (although it has also utilized lunar module descents and ascents), the second incorporates its own artificial explosive sources and an array of geophones. There are two such sources—a “thumper” device operated by the astronauts during their presence on the Moon and a package containing four grenades which may be launched by rocket following an instruction from Earth. The grenades have not yet been released because of the dangers to other lunar experiments not yet complete; but the Apollo 14 astronauts operated the thumper thirteen times out of a possible twenty-one.

The purpose of the ASE, the first results of which have now been reported by Watkins (J.) and Kovach (*Science*, **175**, 1244; 1972), was to determine the surface structure of the Moon down to a depth of about 460 m; and this aim has been achieved within the limits of interpretation imposed by the basic data. The explosive seismic refraction data thus indicate that the immediate surface layer (layer A) of the Moon is 8.5 m thick beneath the geophone array at the Apollo 14 site and has a compressional wave velocity of 104 m s^{-1} .

Because this velocity is typical of a porous and highly brecciated rock material, Watkins and Kovach conclude that layer A is the lunar regolith which, in this region, probably comprises chiefly overlapping ejecta sheets from post-Fra Mauro craters.

Layer B, which lies below layer A but which is distinct from the material below (layer C), has a compressional wave velocity of 299 m s^{-1} although its thickness cannot be determined precisely from the ASE because the velocity of compressional waves in layer C is unknown. But limits may be set for the thickness of layer B. If, on the other hand, the velocity in layer C is to be infinite, calculations show that the maximum thickness of layer B must be 76 m. On the other hand, if it is assumed that the critical distance for the arrival of the head wave travelling through layer C is that to the end of the geophone line (100 m), the minimum velocity of compressional waves in layer C is 370 m s^{-1} and the minimum thickness of layer B turns out to be 16 m.

The fact that layer B is a seismically distinct layer with well defined boundaries suggests that it is also physically distinct from the layers above and below it; but its precise nature is not clear. There seem to be two principal possibilities—that layer B is what Offield (US Geologic Survey Map ORB-III-S-23(25); 1970) identified as smooth terrain material “similar to nearby plains material of presumed volcanic origin” or the Fra Mauro Formation which comprises “material of ejecta blanket surrounding the Imbrium basin”.

In an attempt to decide between these alternatives, Watkins and Kovach have tried to estimate the thickness of the overlapping ejecta sheets from post-Fra

Mauro craters (that is, craters younger than the Fra Mauro Formation) which are thought to form the lunar regolith in the Apollo site region. The regolith thickness thus calculated turns out to be 3.9 to 7.2 m, which must be seen in the light of a previous estimate of the thickness of the Fra Mauro Formation of 5.5 to 15.6 m (Hu and Watkins, *Trans. Amer. Geophys. Union*, **52**, 273; 1971). The maximum thickness obtained from these calculations thus compares well with, respectively, the thickness of layer A and the minimum thickness of layer B derived from the ASE.

This would seem to suggest that layer B is, in fact, the Fra Mauro Formation except that the volcanic interpretation cannot so easily be rejected. For example, Watkins and Kovach estimate the porosity of layer B to be 35–55 per cent, a range which includes various terrestrial analogues of the possible nature of layer B. Thus although the ejecta sheet from Meteor Crater has a porosity of 40 per cent, rhyolite ash and lapilli from the Mono Craters in California have a porosity of 46 per cent and the S.P. andesitic lava flow of Arizona has a porosity of 56 per cent. In short, volcanics as well as ejecta sheets have porosities comparable with those of layer B—a similarity which also extends to compressional wave velocities.

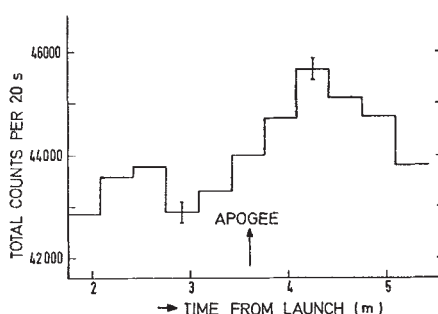
Even so, Watkins and Kovach conclude that, on balance, layer B is more likely to be the Fra Mauro Formation. For one thing, although several young craters in the Apollo 14 site region have penetrated layer B, the Apollo 14 astronauts found very few igneous rocks in the vicinity—a fact which militates against a volcanic nature for layer B.

More Variations from Sco X-1

Sco X-1 has now been seen to vary at X-ray frequencies on a time scale of $\sim 1 \text{ min}$. In next Monday's *Nature Physical Science* (April 17) R. E. Griffiths and B. A. Cooke report an analysis of observations which were made with proportional detectors on the same two rocket flights that carried the counters designed to detect the FeXXV line, suspected of being present in the spectrum of Sco X-1 (*Nature Physical Science*, **229**, 175; and **231**, 136; 1971).

The essence of this analysis is that during the first flight the intensity of the source at 4 to 14 keV was constant for 140 s and then fell by about 2 per cent over 80 s. On the second flight, the energy in the range 2 to 14 keV was steady for about 3 min, then rose by 5 per cent before beginning to fall again, all within the last minute of observation (see figure).

Griffiths and Cooke point out that these time scales are far greater than the expected cooling time of the plasma in which the X-rays originate (a few tenths of a second); they conclude that the presence of these $\sim 1 \text{ min}$ fluctuations supports the idea that mass motions or vibrations of the emitting plasma are responsible for the optical and X-ray flickering.



MITOCHONDRIAL DNA

Models of Replication

from our Cell Biology Correspondent

JUST as seeing a favourite dish in an otherwise chips-with-everything menu whets the appetite and sharpens expectancy, so seeing in the contents list of a journal a report from Vinograd's laboratory makes one tolerant of any amount of mediocrity that might surround it. For Vinograd is nothing if not a professional who always executes his experiments and extracts every ounce of information from their results in an exemplary fashion. Anybody who reads the latest report by Robberson, Kasamatsu and Vinograd in the current *Proceedings of the US National Academy of Sciences* (69, 737; 1972) will not be disappointed.

Last autumn this same group reported (*ibid.*, 68, 2252; 1971) the presence of so-called displacement loop molecules in a population of DNA molecules isolated from the mitochondria of exponentially dividing mouse L cells. Under the electron microscope these molecules can be seen to consist of a short DNA chain hydrogen bonded to the light parental chain of the circular mitochondrial DNA with the corresponding region of the heavy parental chain displaced. Vinograd and his colleagues interpreted these displacement loop molecules as being at the early stages of replication. They have now examined the various molecules that can be found after mitochondrial DNA from exponentially dividing cells has been extracted and fractionated on ethidium bromide—caesium chloride buoyant density gradients, and they have arranged these molecules in a sequence which leads to the formulation of a displacement loop model of mitochondrial DNA replication.

As Robberson *et al.* report, molecules in which the displaced loop of parental heavy strand ranges in size from 10 per cent to greater than 90 per cent of the length of the genome can be seen. Moreover when the displaced, parental, heavy strand exceeds 60 per cent of the genome length it is found to be partially double stranded. In other words, once 60 per cent of the heavy strand has been displaced it seems to act as template for the synthesis of a progeny light strand. This means that the synthesis of the two strands of mitochondrial DNA is highly asynchronous, and not until some 60 per cent of a new progeny heavy strand has been made is the synthesis of the progeny light strand initiated. It is also clear that there is more than one initiation site for synthesis of progeny light strands, but none of these sites becomes available until 60 per cent of the parental heavy strand is displaced

If the two strands are made at roughly the same rate the progeny heavy strand will, of course, be completed long before the progeny light strand, and the liberation of one completed daughter molecule should be accompanied by the liberation of a still replicating molecule, the displaced parental heavy strand and the still replicating progeny light strand. Under the electron microscope such molecules would appear as partially double stranded circles with a single strand region of varying length, and Robberson and his colleagues have observed just such molecules which they have called gapped circular molecules. By hybridization they have proved that in displaced loop molecules it is the parental heavy strand that is displaced and in gapped circular molecules it is again the parental heavy strand which occupies the single strand region, and is therefore acting as template for synthesis of a progeny light strand.

In short, Vinograd's group envisage that the replication of mitochondrial DNA begins at a fixed origin with a single replication fork moving round the parental light strand, making a progeny heavy strand and displacing the parental heavy strand. Not until 60 per cent of the latter strand has been displaced is synthesis of a progeny light strand initiated and completion of the

progeny light strand occurs after the two parental chains have separated. Whether other circular genomes which replicate in eukaryotic cells—for example, polyoma virus of SV40 genomes—behave in this way remains to be seen.

ANIMAL BEHAVIOUR

Mimetic Fishes

from our Marine Vertebrate Correspondent

REPORTS of mimicry among fishes are uncommon. This is perhaps more a result of the difficulty of observation underwater than on account of a scarcity of mimetic behaviour among fishes, for since underwater swimming apparatus has been widely available to biologists the number of reports has significantly increased, as is now shown by two recent articles, both the result of underwater observations.

Young specimens of the tropical Indo-Pacific genus *Platax* (batfishes) are known to mimic in form and swimming habit objects of little interest to predators. Juvenile *Platax orbicularis*, for example, have been observed off the Society Islands drifting on their sides among floating yellowish leaves of *Hibiscus tileaceus* which they resemble most closely. John E. Randall and Alan

Origin of SV40 DNA Replication

IN 1961 when the direction of growth of polypeptide chains during protein synthesis was a matter of dispute, Dintzis performed a classic and ingenious experiment which proved that the synthesis of globin chains is initiated at the amino terminal end and completed at the carboxy terminus. His experiment involved pulse labelling nascent and newly initiated globin molecules, and then analysing the pattern of labelled peptides obtained after digesting the variously labelled protein molecules. From the gradient of labelling of the peptides Dintzis established that the C terminal region of the globin molecule is synthesized after the N terminal region.

Nathans and Danna, as they report in next Wednesday's *Nature New Biology* (April 19), have now adapted this experimental rationale to the analysis of the replication of the double stranded, covalently circular DNA genome of SV40 virus in BSC-1 cells, and have shown that the replication of this DNA is initiated at a specific origin rather than at random anywhere in the molecule.

The secret of Nathans and Danna's success lies in their exploitation of a bacterial restriction endonuclease obtained from *Haemophilus influenzae* which, as they have previously shown,

digests SV40 DNA to yield eleven fragments, at least eight of which appear in amounts equimolar to the initial amount of intact SV40 DNA. They argued that if the replication of SV40 DNA is initiated at a unique or preferred site by varying the length of pulses of ³H-thymidine, it should be possible to label preferentially either the first part of the molecule to be replicated or the last part to be replicated. In short, just as Dintzis was able to show a gradient of labelling of globin molecules, the synthesis of which is initiated at a unique point, so they should be able to predict a gradient of labelling of the fragments of newly replicated SV40 DNA that are liberated by the *H. influenzae* endonuclease.

When Nathans and Danna digested variously labelled SV40 DNA molecules, sure enough they found a gradient of labelling as predicted. This finding confirms the assumption that the replication of SV40 DNA molecules begins at least at a preferred if not a unique site. They also estimate that under their conditions the whole molecule is replicated in about 5 minutes, and they point out that by refining their technique it may be possible to decide whether or not the replication proceeds in both or only one direction about the circular molecule.

R. Emery (*Zoologica*, **56**, 115; 1971) now report that juveniles of another species of batfish, *P. pinnatus*, show a remarkable resemblance to turbellarian flatworms.

The young *P. pinnatus* is deep bodied with high dorsal and anal fins and its body is coloured black with the outline of the fins picked out in bright orange. Turbellarians often have a brightly coloured border, and at least two Pacific forms have a broad orange margin. Similar coloration is shown by some nudibranchs, which like the flatworms are known to be distasteful, if not actually toxic, to fishes. The juvenile batfish, however, improves on the mimetic effects of coloration and body form by swimming on its side, gently undulating its fins, thus imitating the swimming movements of its presumptive models. Whether this mimicry is sufficient to deter predators from eating the young *Platax* is not known, but Randall and Emery, both experienced underwater biologists, admit to being misled on first sight by the fish's resemblance to a flatworm.

Similarly, Victor G. Springer and William F. Smith-Vaniz (*Smithson. Contrib. Zool.*, No. 112, 1; 1972) have independently confused two blennioid fishes as one species, or have been misled by mixtures of species in supposedly sorted museum collections, as a result of the very close similarities in body form and coloration between two or more species. Springer and Smith-Vaniz were later able to supplement these more or less casual observations by detailed underwater observation and laboratory experiments in the Red Sea and Gulf of Aqaba.

Although these authors discuss other mimetic relationships in the blenny family the greater part of their article is taken up by discussion of a mimetic complex involving three species in this region: *Meiacanthus nigrolineatus*, a blenny with a blue to blue-grey head and anterior body, but yellowish posterior body, with a black lengthwise stripe on the body; *Ecsenius gravieri*, which is similarly coloured; and *Plagiotremus townsendi* which differs from the other two chiefly in having a horizontal white bar passing round the tip of the snout. It seems certain that *Meiacanthus nigrolineatus* is the model for the other two; it seems to be slightly more common than *E. gravieri*, and much more abundant than *P. townsendi*.

More significantly Springer and Smith-Vaniz discovered that on each side of the lower jaw of *Meiacanthus* there is a massive canine tooth with a deep groove along its anterior surface and with glandular tissue occupying a depression in the dentary bone. Pressure in the vicinity of the gland produces a ready flow of milky fluid from the canine tooth groove, and histological

examination strongly suggests it to be a venom producing organ. (A specimen was induced to bite the junior author's midriff where the bite produced an irregular reddened area and later a pale welt!) Other tests involved offering *Meiacanthus* to captive native predatory fishes and naïve imports from the Mediterranean. Most of the native species could not be induced to eat this blenny, or they released it very quickly after it was ingested. The Mediterranean predators (which cannot normally encounter *Meiacanthus*) quickly learned to reject it.

Springer and Smith-Vaniz's studies suggest that *Ecsenius*, which lacks venom glands and grooved canines, and is acceptable prey to larger fish-eating fishes, is primarily a Batesian mimic of the noxious *Meiacanthus*. *Plagiotremus townsendi* is presumed to enjoy a similar relative immunity to attacks by predators on account of its general resemblance to *Meiacanthus*, but the relationship is more complicated. Both *Meiacanthus* and *Ecsenius* are non-aggressive species which feed primarily on small invertebrates and for this and the unpalatable nature of the first fish they are allowed close to larger fishes. *Plagiotremus townsendi*, however, feeds on the mucus, epidermal tissue and scales of other fishes, and Springer and Smith-Vaniz report it as attacking a wide range of non-piscivorous scaled fishes in the Red Sea. It thus seems more likely that in addition to deriving protection by its resemblance to the unpalatable *Meiacanthus*, *P. townsendi* uses the non-aggressive nature of both *Meiacanthus* and *Ecsenius* as a Trojan horse to approach its own prey. The relationship of these three species is thus a complex of different forms of mimicry.

ACOUSTIC EMISSION

First British Symposium

from a Correspondent

ALTHOUGH the role of acoustic emission in determining the size and location of earthquakes is well known, its potential for monitoring the behaviour of materials and engineering structures has only recently become widely appreciated. The feeble stress waves generated in materials by processes such as cracking and dislocation movement may be amplified, detected and recorded to provide the basis of a very powerful non-destructive testing tool. To find out what acoustic emission is all about and what it can do, an unexpectedly large number of people attended a meeting organized by the Institute of Physics on March 14 at Imperial College, London.

The two principal areas of application are in the field of materials research and non-destructive testing of large

engineering structures. In this last role the technique has already been used to examine large steel pressure vessels for the presence and actual location of cracks and defects. A system capable of providing such important information is computer-controlled and could cost from £35,000 upwards, and requires an operator with knowledge and ability in many branches of science and engineering, but the cost of catastrophic failure may frequently be inestimable.

In addition to the current applications which largely involve proof-testing pressure vessels, large gas pipes, and the like, the continuous surveillance of acoustic emissions from structures, mines, dams, earth and snow slopes will provide an early warning system which is badly needed. The ability to detect dynamic microscopic events in materials also provides a potentially useful experimental facility for measuring plastic deformation, microcracking, debonding of interfaces, hydrogen embrittlement and stress corrosion cracking, and this is becoming increasingly apparent to the materials scientist. The attention of a wide cross-section of the industrial community has been drawn towards the inherently attractive notion of listening to materials and structures "playing their own signature tunes", coupled with the potential power of the technique in so many applied problems.

There were a few contributions at the meeting on the technological implications of this technique and some detailed reports about the various aspects of detector design, noise problems, and materials research. Introductory lectures were given by Dr A. A. Pollock (Cambridge Consultants Ltd) and Dr H. Dunegan (Dunegan Research Corporation, California). Some flaw location systems and applications were described in detail by Dr D. Birchon (Admiralty Materials Laboratory, Poole) and Dr D. L. Parry (Jersey Nuclear Company, Washington). Dr G. J. Curtis (Non-Destructive Testing Centre, Harwell) presented some recent results of adhesion tests which use broad bandwidth transducers.

Acoustic emission is still a very young subject, especially in Britain, and this first symposium was essentially nothing more than a progress report. The problem is that it is frequently difficult to determine in which direction the subject is progressing and exactly what the "end product" is likely to look like. The level of research and development effort in Britain is certainly very small in comparison with the level of industrial interest, if that is to be gauged by the number of people attending this meeting. It has now been demonstrated that acoustic emission is something more than a scientific curiosity with many future developments and applications to be anticipated.

Raw Materials and the Price Mechanism

JOHN MADDOX

This article, the second in a series on the environment, deals with the way in which price and demand are likely to shape the future availability of raw materials.

THE problem of mineral resources has played a central part in discussions of the environmental crisis, not merely in the past few years but in the nineteenth century. The essence of the case was first put by Malthus especially in connexion with food supplies and the availability of land. "Man is necessarily confined in room. When acre has been added to acre till all the fertile land is occupied, the yearly increase of food must depend upon the melioration of the land already in possession. This is a fund, which, from the nature of all soils, instead of increasing, must be gradually diminishing." (Malthus, *Essay on Population*, sixth edition.)

Although Malthus himself did not deal with the problems of depletion which exercised economists later in the nineteenth century, his was the first forceful statement of the contradiction which there must be between growth of a population or of a demand for resources and what appears to be the limited extent of possible exploitation. Barnett and Morse¹ have, however, argued that "At an unsophisticated level of thought, it is sometimes taken for granted that fixity of natural resources and an expanding population—the two fundamental Malthusian postulates—suffice to produce diminishing returns, but this is incorrect." In particular, they say, the Malthusian conflict must be qualified by a consideration of the rates of increase and the availability of natural resources and the ease (and cost) of extracting them.

Including Economics

The essential simplification in the Malthusian view is that it assumes that there will be no changes other than the growth of the demand for food, land or other natural resources. A more particular weakness of the argument is that it overlooks considerations in economics. In the early nineteenth century, Ricardo had pointed out that scarcity is not absolute. From the beginning of the exploitation of a resource, scarcity becomes more apparent, with the result that the cost of extracting each extra unit of output from a mine continually increases. This doctrine of diminishing returns is not merely plausible but valid in many real situations. For example, increasing the yield of crops from a field usually requires more intensive agriculture, either in the application of fertilizers or in the improvement of the seeds. And the cost (measured in man hours of effort or by some other statistic linked to the productive effort required for extraction) of extracting coal from a mine increases as shafts are deepened or roadways lengthened.

Even this plausible doctrine of diminishing returns was heavily qualified in the nineteenth century by those such as John Stuart Mill, who pointed out that the proposed monotonic increase of unit cost with the continued exploitation of a finite resource would be undermined by new discoveries or by technical progress—"by whatever adds to the general power of mankind over nature; and especially by any extension of their knowledge, and their consequent command, of

the properties and powers of natural agents". Wherever the truth lies, there can surely be no dispute that in the assessment of the scarcity of natural resources, absolute quantities are less important than economic costs. After all, it remains the simple truth that the aluminium in the top kilometre of the Earth's crust amounts to 2.65×10^{17} metric tons, or the equivalent of 70 million tons for every person now alive. Although aluminium is the most abundant of all metals, even quite scarce materials are quite abundant by standards such as these—sea water contains 10^{10} tons of gold, for example, and upwards of 2.5×10^7 tons of mercury, or 2,500 times as much as the present annual production of mercury. In circumstances like these, it is clear that the absolute physical limits on resources are less important than the economic limitations. What matters is the economic cost of extracting them and putting them to use. It is only fair to acknowledge that economic scarcity could be crippling before the absolute limits of the surface of the Earth are reached. (In passing, it may similarly be argued that in a community in which all but a small proportion of the labour force is compelled to work on the land, there may be an economic scarcity of food even though there may be plenty of extra land still to be cultivated.)

By the same reasoning, however, it is not permissible to use current estimates of the economically exploitable reserves of metal ores, or of petroleum, as a basis for calculating how long these will last. This, unfortunately, is the basis for most of the recent gloomy estimates of the potential scarcity of raw materials. On this basis, for example, lead is quickly discovered to be potentially scarce. According to the US Bureau of Mines² there are known reserves of 30 million metric tons of lead in known deposits in the United States which could be mined economically at a price of 17 cents

Table 1 World Production of Metals in 1969

Metal	World production million metric tons
Aluminium	9.1
Copper	6.6
Iron, pig	420
Lead	3.25
Magnesium	0.202
Steel, ingots and castings	580
Tin	0.232
Uranium oxide	19.7
Zinc	5.1

Taken from refs. 3 and 7.

a pound or less, and the rest of the world has known reserves of 60 million tons of lead. With annual production of lead running at 3.25 million metric tons (in 1969, Table 1 and refs. 3 and 7) this implies that known reserves of lead ore will last only until about the end of the present century, even at the present rate of consumption (and the experience of the 1960s suggests that lead consumption is growing at a rate of 3 per cent a year). But it is also clear that the presently known reserves of lead are likely to be augmented substantially in the next few years as wider use is made of the new techniques of geophysical exploration. There have been spectacular successes in the past few years in North America, where new techniques have identified no fewer than 30 million tons of lead in ore deposits in Missouri, and upwards of 10 million tons in New Brunswick, Canada. Ireland has become a source of lead again for the same reasons. And

Table 2 Dates of Exhaustion of Known Reserves

Metal	Date of exhaustion
Uranium-235	1985
Tungsten	2005
Copper	2000
Lead	1987
Zinc	1988
Tin	1990
Gold	1988
Silver	1988
Platinum	1988

is it likely that economically minable lead ores are equally distributed between North America and the rest of the world? In short, simple arithmetical calculations of the point at which reserves will be exhausted are, at present, more an incentive to exploration than a sign of real scarcity.

Table 2, based on a diagram due to Cloud⁴, shows the dates at which known reserves of certain minerals are likely to be exhausted at present rates of consumption. Cloud points out that these estimates take no account of the way in which increases of the prices of the materials concerned will bring ores which are not now economic into production, no account of future discoveries of raw materials, no account of the way in which price changes will encourage the recycling of stocks of materials now in use, and no account of the feasibility of the substitution of comparatively plentiful materials for those now in use. Unfortunately, his followers have been less discriminating (see ref. 5).

Quality of Ores

In reality, however, it is not surprising that the known reserves of ores which can be mined, turned into metal and then sold at present prices should be comparatively short-lived. In the nature of things, the mining industry will first of all exploit the richest ores which are accessible. Moreover, when that has been done, if new discoveries do not add to the reserves of richer ore, then there is almost certain to be a relative increase of price, when it will be economic to bring poorer quality ore into production. In the circumstances, it is clear that the important questions are how the exploitable reserves of important raw materials are likely to change with time, and how demand for them is likely to be affected by changes of market price, which could profoundly affect the ways in which materials such as copper and zinc are used. For geological and economic reasons, each raw material must be dealt with separately. Historical evidence is as relevant as geophysical speculation.

For most materials, the experience of the past century would suggest that the effects of scarcity are not merely remote but even undetectable. In the years since 1870 in the United States, for example, the prices of most raw materials have not increased but, on the contrary, have decreased, while production has grown rapidly. Between 1870 and 1960, the output of the mineral industry in the United States increased by a factor of forty, but the cost of extraction, measured in terms of the numbers of man

hours worked in the extraction industries and the amounts of capital employed, has steadily decreased, by 3.2 per cent per year in the past half century¹.

What these gross figures imply is that in the extractive industries of the United States, in many ways representative of the rest of the world, the depletion of resources and the simple Ricardian prospect of diminishing returns has been more than offset by increases of efficiency in the extractive industries. The case is well illustrated by copper, an important ingredient in technology since the ending of the Stone Age. In the past several years, the richest deposits of copper ore have been progressively exhausted—Cornish copper-mining has, for example, come to an end—and the average grade of copper ore has steadily decreased.

Nevertheless, the world price of copper fell between 1900 and 1933 from 40 cents a pound to 20 cents a pound (measured in 1957 dollars). Since then, the price reduction has been reversed, and the price of copper is again about 40 cents a pound (in 1957 dollars) which is a sign that increasing production efficiency is no longer able to offset the increasing economic cost of mining ores of poorer quality (see Fig. 1). It is, however, relevant to speculate about the future availability and price of copper. On present trends, it seems likely that the world price of copper will increase steadily in the years ahead, possibly from 52 cents a pound in 1970 to between 75 cents a pound and 100 cents a pound by AD 2000. (These estimates of future price trends are due to the US Bureau of Mines² and Lowell⁶, see Fig. 1). In other words, where copper is concerned, the historical evidence suggests that increasing scarcity will indeed be reflected in an increased price of copper before the century is out.

To what extent will the exploitable reserves of copper be increased by such an increase of price? Copper mining has been transformed in the twentieth century from the exploitation of high grade ores containing 6 per cent or more of copper concentrated in narrow veins to the exploitation of porphyry ores with grades of 2 per cent or less. This trend, which has been continuous since 1906, has been a vivid demonstration that the exploitation of vast bodies of low grade ore can be more economic than that of high grade ore in narrow veins. Lowell estimates that of the 3×10^{15} tons of copper in the top mile of the Earth's crust, 10^{10} tons are concentrated in potential ore bodies with a concentration of more than 0.25 per cent of copper, of which 4×10^8 tons have been mined so far, mostly from narrow veins. He estimates that something like 4×10^8 tons of copper exist in mineral deposits of widely disseminated form, either as porphyry copper or in association with magnetite. At the current rate of copper consumption (5.9 million tons in 1969), this potential resource of low grade copper ore is the equivalent of 650 years' supply. It is true, of course, that these estimates may turn out to be too high, but especially now that there is understanding of the way disseminated low grade ores are formed in association with tectonic processes in the Earth's crust, there seems every likelihood that exploration should become cheaper and more efficient. Certainly the copper industry itself does not share the pessimism of commentators such as Cloud.

But will not these comforting projections of potentially exploitable reserves be undermined by the rapid growth of copper consumption to be expected if countries other than the United States continue to develop economically and industrially? Luckily, it is not safe to suppose that the future demand for copper will increase exponentially at recent rates or even that it will be linked to the pace of growth of economic statistics such as GNP (Gross National Product) and GDP (Gross Domestic Product). Already there is evidence that the price mechanism is taking the edge off growth. For example, demand for copper in the United States has faltered in recent years as the price has increased from 31 cents a pound in 1961–63 to more than

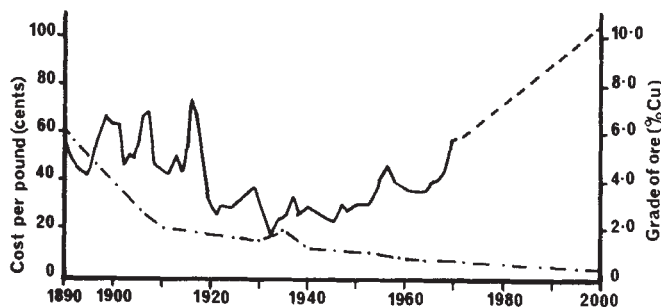


Fig. 1 Average grade of copper ore mined and price of copper (1970 dollars). —, Price; ---, predicted price trend; -.-, grade of ore mined and predicted trend.

50 cents a pound in 1970, and as the incentive to use other metals instead has been increased. Indeed, on the basis of the tendency in copper consumption in the United States between 1963 and 1968, the US Bureau of Mines⁷ estimates that the demand for primary copper (55 per cent of total consumption in 1968) might decline from 1.54 million tons then to 0.46 million tons by the year 2000, but this estimate is probably artificially low because of the strikes which halted domestic copper production in 1967 and 1968. However, the trend of the past twenty years suggests that primary copper consumption in the United States will increase from 1.54 million tons in 1968 to 2.07 million tons by the end of the century, an increase of less than one per cent a year, much slower than the expected growth of the population of the United States.

How much weight should be given to this modest prediction? At present, primary copper accounts for 55 per cent of the annual consumption of copper. The rest consists of scrap of various kinds—an illustration of the extent to which recycling is already a reality in the metallurgical industries. The Bureau of Mines calculates that by the end of the century, the total demand for copper will be somewhere between 8.95 million tons a year and 14.35 million tons a year. It is not possible accurately to forecast the extent to which substitution by other metals—aluminium in electrical applications, for example—will reduce the demand, for everything will depend on the course of the expected increase of the price of copper, but the US Bureau of Mines has calculated that substitution could reduce the total demand for copper in the electrical industries by 47 per cent. By the same test, it is not possible accurately to predict the extent to which recycling will be encouraged by price increases, but the experience of the past few years suggests that primary copper is likely to be a declining proportion of total consumption in the United States in the years ahead. In other countries, where stocks of potential scrap are smaller, it is probable that consumption of primary copper will be more closely linked with economic activity, at least for some years to come.

Partly because of uncertainties about the likely growth of industrial development and partly because it cannot easily be predicted how the rising price of copper is likely to affect the pattern of use of metal in developing countries, estimates of future demand are bound to be uncertain. On assumptions about the speed with which growth will increase which range from a compound rate of 3.4 per cent to 5.8 per cent a year, however, the US Bureau of Mines calculates² that the demand for copper outside the United States at the end of the century may be anything between 16.8 million tons and 34.9 millions a year. It goes without saying that these estimates are uncertain not merely because it is impossible to predict the ways in which substitution may affect the pattern of use of metals such as copper in developing countries but also because there may be circumstances in which investment in copper increases even more quickly than present predictions about the growth of industrial production in developing countries.

The demand for copper in developing countries will naturally be determined not merely by the extent to which they follow or avoid the pattern of consumption in countries such as the United States, but the worst case is that in which it is assumed that at some stage in the future the amount of copper consumed in the world as a whole will be determined by present consumption per head in North America, the equivalent of 0.6 kilograms per head per year. Even if the world's population is eventually stabilized at 7,500 million, this would imply an annual consumption of 46.2 million tons of copper a year. At this rate of consumption, it is clear that even if exploration reveals still larger amounts of ore, so that conventional reserves are comparable with the quantities now accessible, the copper industry could survive for only a decade or so.

Prices and Nodules

This calculation is, however, excessively gloomy for two reasons. First, it is inconceivable that the demand for copper could grow to anything like 50 million tons a year without a further steep increase of price and more vigorous attempts to re-use copper. From this point of view, it may be more satisfactory to use as a yardstick for predicting the future demand for copper in the world as a whole not the present annual consumption of new copper in the United States but the total quantity at present locked up in electrical generating machinery, estimated to be 40 million tons. On this standard, the world as a whole would need to accumulate stocks of 1,200 million tons of copper at the point at which the population had stabilized, a figure not altogether out of line with the likely conventional reserves of copper minable at the price of 75 cents or even \$1 a pound. Inevitably, of course, the recycling of copper on such a scale would imply profound changes in the copper industry, but that is merely another way of saying that electricity generating equipment will become more expensive (unless the rising price of copper is cancelled out by improvements in the efficiency of design) and that copper would no longer be used except where it is essential.

The second qualification of the most gloomy predictions about the future is that the exploitable reserves of the metal may be enormously increased when it becomes possible to extract copper from the manganese nodules which appear to cover substantial tracts of the deep ocean bed at depths of 5,000 metres or so. At present, of course, it is unclear how quickly these reserves will be brought into use. Evidently the problems of recovering these materials are formidable, at least in comparison with the problems of extracting copper from open pits in the surface of the Earth, yet the obstacles to the recovery of copper from this vast resource are at present largely metallurgical. The problem is that of recovering copper, nickel and cobalt from silicates, and it is too soon to predict what the cost of processes like this will be. The only certainty is that there must be some low price at which recovery is economic. When that price is reached, very much larger reserves of copper than those now considered accessible will be used.

The changing pattern of the world copper industry is thus an illustration first of the unavoidable complexity of all attempts to forecast the likely course of supply and demand. It also points to some of the ways in which gradual increases of the price of copper are an incentive for exploration and for substitution and recycling.

Mercury and Tin

Exactly similar tendencies of increasing price and the growth of recycling are to be found in the recent economic history of other metals thought to be on the edge of scarcity. Mercury is a good example. Mercury ores occur chiefly in regions of Tertiary volcanism. For much of the industrial history of the world, mercury has come from four regions—Spain, Yugoslavia, Italy and California. In the early 1960s, the US Bureau of Mines estimated that American reserves of mercury were 140,000 flasks (each amounting to 76 pounds) at a price of \$200 a flask, but roughly six times as much (\$27,000 flasks) at a price of \$500 a flask. Annual consumption in the world as a whole amounted to 200,000 flasks per year in 1968, 37 per cent of it in the United States, and it is clear that even at this rate the accessible reserves would last only for two decades. One result has been a sharp increase of price, which was less than \$300 a flask in the early 1960s but which is now more than \$600 per flask. Like copper, mercury is bound to become increasingly expensive—the US Bureau of Mines estimates that the price may be \$1,500 a flask by the year 2000.

It is no surprise that in the United States there has also

been a stagnation of the demand for mercury, where 73,000 flasks were used in 1965 and 79,000 in 1969. Most of the growth of demand has been in the chemical industry, where large quantities are used in the electrolytic preparation of chlorine and caustic soda (20,700 flasks in 1969) but other uses have been declining—the use of fungicides and pesticides based on mercury is, for example, decreasing rapidly. And in spite of the advantages of mercury in electrolytic apparatus and storage batteries, there is no reason why these uses should not diminish as the price of mercury increases. Nickel cadmium batteries, for example, can confidently be expected to replace mercury batteries, while caustic soda cells based on the use of diaphragms will progressively take over from electrolytic cells using mercury. Moreover, it is now economic to recover mercury from the dust collected in factories making use of mercury—a procedure which is in any case necessary on grounds of occupational health. The result is that forward predictions of annual demand are necessarily extremely hazardous. In short, it is entirely conceivable that demand for mercury in the United States will not increase substantially between now and the end of the century and that it may even decline. Elsewhere in the world, the price of the metal will be so great that mercury is unlikely ever to be used as intensively as at present in the advanced countries of the world.

The consequences of increasing scarcity are less apparent with other important metals. Tin is high on most lists of scarce materials and, indeed, prices fluctuate considerably in spite of the buffer stocks maintained by the International Tin Council, but it does appear that the price (in constant money terms) has doubled since the 1930s. The US Bureau of Mines forecasts a further price increase by the end of the century, from \$1.48 a pound in 1968 to \$1.90 a pound in 2000. In the United States, however, over the past twenty years, the consumption of tin has been substantially constant, and the Bureau of Mines' forecast that US consumption of tin will increase from 59,000 tons (in 1968) to between 71,000 tons and 98,000 tons in 2000 is based on the assumption that the International Tin Council will succeed in its objective of finding important new uses for the metal. In reality, however, the biggest imponderable is the uncertainty about the future supply of tin ores. World reserves have been estimated at 4,330 thousand tons at a price equivalent to \$1.60 a pound, enough for only 22 years at the present rate of consumption, but it seems to be agreed that tin should occur in disseminated ore deposits substantially similar in their mode of formation and distribution to the copper porphyry ores. If those expectations are borne out, potential supply would be sharply increased, and the rising price trend could even be reversed. Already the same processes have taken the edge off what seemed to be the increasing scarcity of metal a decade or so ago.

Larger Reserves

It goes without saying that where metals such as magnesium are concerned, accessible reserves are for all practical purposes inexhaustible. The US Bureau of Mines estimates that a ten-fold increase of demand would have no significant effect on price, which is closely linked with the cost of the electricity used in electrolytic extraction. The Great Salt Lake in Utah contains an estimated 640 million tons of magnesium chloride, and is now being used as a feed for electrolytic magnesium plants. In the United States, consumption is thought likely to grow at 2.0 per cent a year in the remaining decades of this century, but elsewhere the rate of growth may be 6.0 per cent a year. Plainly there need be no absolute shortage of structural materials for the light engineering industry.

In circumstances like these, it is clearly impossible to take arithmetical calculations of the longevity of mineral deposits at their face value. Even metals such as lead and

Table 3 Abundance, Geological Concentratability and Price of Some Economic Metals

Metal	Primary abundance	Ore grade p.p.m.	Factor of concentration	Price cents per pound	Price (cents per pound) × abundance (p.p.m.)
Nickel	100–1,000 (basic rock)	10,000	10 to 100	100	10–100,000
Zinc	80	100,000	1,000	14	1,100
Copper	70	10,000	100 to 200	50	3,500
Columbium	24	20,000	1,000	150	3,000
Cobalt	23	—	—	180	3,600
Lead	16	64,000	4,000	14	224
Tin	3	3,000	1,000	150	300
Uranium	2.5	1,000	400	700	1,750
Molybdenum	1.5	1,500	1,000	170	250
Silver	1.0	500	500	2,500	2,500

zinc, supposedly threatened with extinction by 1988 or thereabouts, have remained remarkably constant in price (in real terms) over the past three decades, chiefly because the discovery of new reserves has made up for the quite rapid increase of consumption which there has been. Among the missing components in the arithmetical calculations of scarcity is the lack of a clear appreciation of how geochemical and geophysical exploration can be expected to contribute new reserves. One striking feature of the successful record of prospectors in the past few years has been the way in which discoveries of new ore bodies have sprung almost directly from geological insight into the mechanism of their formation—the formation of zinc ores in association with submarine volcanism in the past has, for example, been a powerful tool in recent discoveries. Table 3 (see ref. 7) shows that there is a measure of regularity in the relationship between present prices of important metals and their geochemical abundance which is, in itself, a sign that the metallurgical industries are able to win raw materials as if from the Earth's crust as a whole.

In the argument about the adequacy of natural resources, it is therefore important that the question should be properly framed. As in the past 5,000 years, there is bound to be a continuing realignment of the relative supplies of economically important raw materials. The question to be asked is whether, at some point in this process, the pattern of industrial activity will be seriously affected by the way in which the relatively scarcity of some widely used materials may force manufacturers and their customers into inconvenient substitutes. Where metals are used for structural purposes, substitution is of course comparatively easy to arrange. Where materials such as copper are valued for their electrical properties, it is perhaps fortunate that aluminium will always be a potential safeguard against scarcity. And it is also fortunate that where materials such as mercury are valued for their chemical properties, as in catalysis, the quantities involved are relatively small. It does not follow from this, of course, that there is no need to be concerned about the management of natural resources—good planning in advance could evidently bring great economic benefits. With many materials, it would be helpful if governments or international authorities were to intervene with devices which, for example, might help to stabilize the prices of metals where scarcity is a real threat.

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Search for Antimatter in Primary Cosmic Rays

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A new upper limit on the amount of antimatter in primary cosmic rays has been established. The limits are considerably lower than those for any previous experiment.

THE symmetry between matter and antimatter observed at accelerators has led many astrophysicists¹⁻³ to suppose that there is a similar balance in the universe. If, however, matter and antimatter were mixed, considerable annihilation reactions would occur. Gamma-ray measurements⁴ set a stringent upper limit on any mixing of matter and antimatter within our galaxy. Although Alfvén⁵ has advanced a mechanism which might permit regions of matter and of antimatter to coexist within our galaxy without appreciable mixing, it is also possible that matter and antimatter are concentrated in whole galaxies, in which case, if the early state of the universe were homogeneous, there would have to be a mechanism for separating matter and antimatter into galaxies.

In either case, one way of discovering that regions of antimatter exist elsewhere in the universe would be the unambiguous detection of antimatter nuclei in the primary cosmic rays. It is probable that a small flux of antiprotons (about 10^{-5} of the proton flux⁶) would be produced by cosmic-ray interactions with the interstellar gas, but these reactions should produce negligible fluxes of anti-helium and the more complex anti-elements. Therefore, observation of complex anti-nuclei such as helium, carbon or oxygen would almost certainly imply the existence of antimatter stars capable of nucleosynthesis.

Several teams have searched for antimatter⁷⁻¹³. The most stringent experimental upper limits for antimatter flux have been set by searches in large emulsion blocks that have been exposed at high altitudes to the incident cosmic rays. Examination of several thousand stopping cosmic-ray nuclei of charge greater than 2 showed no events with the characteristic annihilation products at the termination of the track. As Greenhill *et al.*⁷ pointed out, however, these measurements apply only to low-energy antimatter flux, and it is reasonable to expect that antimatter might become more plentiful at higher energy. The observation of just one or two well verified, unambiguous anti-nuclei in the incident cosmic-ray flux would have profound astrophysical significance, because most present day cosmologies do not take account of significant amounts of antimatter.

In this article we report the first data from two flights of a new superconducting magnetic spectrometer, which was capable of a direct matter-antimatter separation in the cosmic rays. Antimatter events would appear in the spectrometer as trajectories which curve in the opposite direction to common matter, because of their negative charge. A detailed description of our equipment is given elsewhere¹⁴. Fig. 1 presents a schematic diagram and Table 1 summarizes some of the properties of the instrument.

Table 1 Specifications of the Magnetic Spectrometer

Flight dates	September 18, 1970, and May 8, 1971
Mean magnetic field integral	3.8 kG m (first flight) 4.3 kG m (second flight)
Spatial detectors	Four optically viewed spark chambers, four 1-cm gaps each
Optical reconstruction error	± 0.14 mm per spark chamber
Maximum detectable rigidity (set by optics and field integral)	75 GV/c (first flight) 90 GV/c (second flight)
Scattering material with the spectrometer	4.12 g/cm ² , 0.25 radiation lengths (first flight) 2.04 g/cm ² , 0.055 radiation lengths (second flight)
Geometry factor	660 cm ² ster
Trigger counters	Pilot B and Y plastic scintillators
Time-of-flight measurement	With helium incident, timing error = ± 4 ns giving rejection of > 95% against albedo events With $Z > 2$ incident, timing error = ± 2.5 ns giving rejection of > 99% against albedo events
Charge resolution (helium through oxygen)	± 0.15 charge, by recording light levels in the three trigger scintillators
Trigger threshold	Selectable to gather data with charge Z greater than or equal to 1, 2, or 3
Residual atmosphere for flights	Roughly 5 g/cm ² of air left above the instrument
Data-taking times	2.5 h with $Z \geq 2$ and 13 h with $Z \geq 3$

The spark locations and scintillator pulse height data were recorded on photographic film. All sparks were automatically measured on a cathode-ray tube encoding machine, and all pictures were visually scanned. Events showing occasional delta-ray activity in the spark chambers were redisplayed on a cathode-ray tube, and a scanner rejected the spurious tracks. Multiprong interactions in the apparatus and other back-

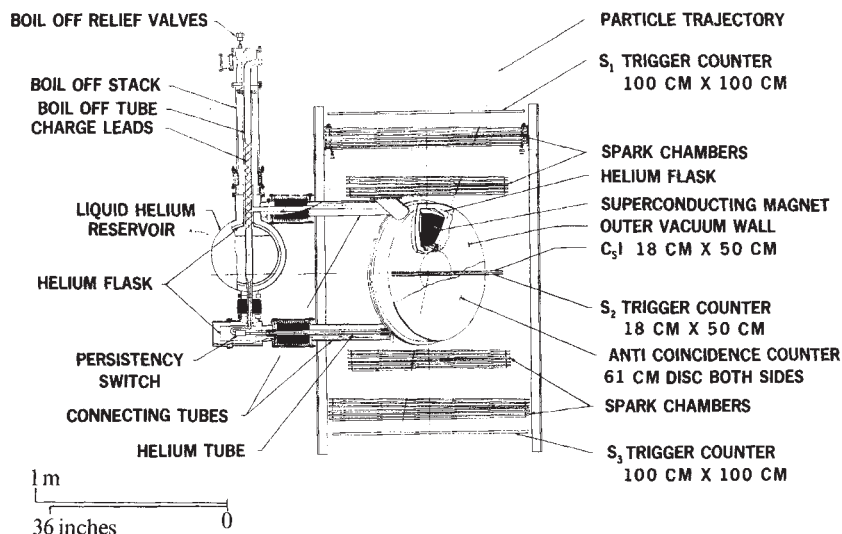


Fig. 1 Schematic SSCM detectors and cryogenics.

ground events were rejected after measurement. We fitted each good event to a curved trajectory through the magnetic field, and calculated its specific curvature K ($=1/\text{rigidity}$) and goodness of fit χ . Poorly fitting events were eliminated using a χ -cut, which should reject only 3% of the good data. Fig. 2 shows a specific curvature distribution for a sample of the fitted data. The maximum rigidity detectable with the automatic measuring machine was about 50 GV/c. A large body of common matter events starts at $K=0$ and extends beyond the end of the graph to geomagnetic cutoff at $K \approx 0.25$ (c/GV). Any potential antimatter signal might be masked by some of the common matter events near $K=0$ spilling over into the region of negative K . Spillover could be due to measurement error or to occasional misinterpretation of an event by our automatic measuring and analysis sequence. Therefore, all events which had K less than zero were remeasured by hand on a machine which had three times the accuracy of the automatic machine. On remeasurement, most of these gave a positive specific curvature, but some remained with negative K and these we regarded as antimatter candidate events.

"straight-through" events which were taken for each flight with the superconducting magnet turned off. Fig. 3 shows the K -distribution for straight-through events in the second flight. The smooth curve is the Monte Carlo fit to these data. For the nuclear scattering, we used a diffraction shape for the angular distribution with a cutoff in total momentum transfer of $\Delta P_{\text{max}} = 300$ MeV/c. Any greater momentum transfer than this in a collision should fragment the incident nucleus. Usually this would cause it to fail our spark chamber topology requirement and to give a much smaller pulse height reading in the bottom scintillator of the apparatus. Nuclear scattering should have contributed several antimatter candidates in the helium portion of our data, but the cutoff on momentum transfer becomes such a stringent limit for higher- Z elements (whose total momentum is Z times the rigidity) that in our $Z \geq 3$ data there are no appreciable antimatter candidates to be expected from this source.

Table 2 Sources of Antimatter Candidates

- (1) Optical reconstruction error moves an event over from $K > 0$ region
- (2) High-energy albedo nucleus simulates negative charge because it is incident from below
- (3) Nuclear scattering in the material of the instrument caused an apparent negative curvature for a common matter event
- (4) An actual antimatter signal

Table 3 presents the antimatter candidates and Monte Carlo predictions for all our data. We have presented helium (with about 9% admixture of higher- Z data) separately from our $Z \geq 3$ data, because the nuclear scattering mechanism is unimportant for the latter. For the distribution of common matter events that could contribute in our Monte Carlo predictions we used also a power law distribution in rigidity, $dN/dR \propto R^{-j}$ where the value for $j=2.6$ was determined by a fit to all our data. A more detailed analysis of the rigidity spectra of our data is now being prepared. In terms of specific curvature, the power law becomes $dN/dK \propto K^{j-2}$. The Monte Carlo predictions of Table 3 are quite sensitive to the value chosen for j . Uncertainty in j causes the overall scale of the values to have an uncertainty of about $\pm 20\%$. No significant enhancement is seen in any of the bins. In the high- Z data no events are seen for $R < 33$ GV/c. This limit and the one set by statistics in the rigidity range between 33 and 100 GV/c are shown in Fig. 4. This figure also

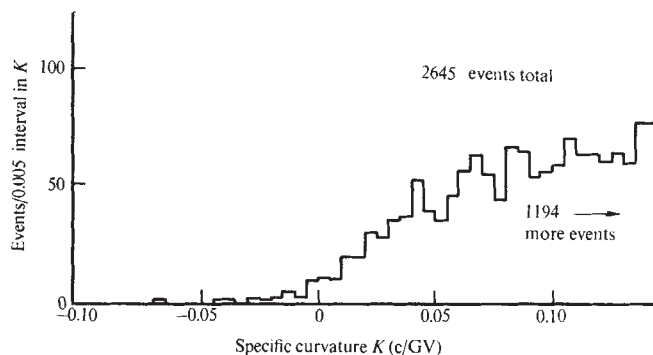


Fig. 2 A plot of specific curvature K distribution for a sample of data from second flight measured automatically. All events with $K < 0$ to be remeasured on a more accurate machine.

Table 2 presents a list of possible explanations for these events. We are able to rule out source 2 as an explanation, because we observed no albedo time-of-flight (a difference in timing of about 10 ns) for any of the antimatter candidates. For sources 1 and 3, we made a Monte Carlo calculation which included the optical error, multiple coulomb scattering and nuclear scattering of our instrument. The optical error was obtained by a detailed study of several hundred

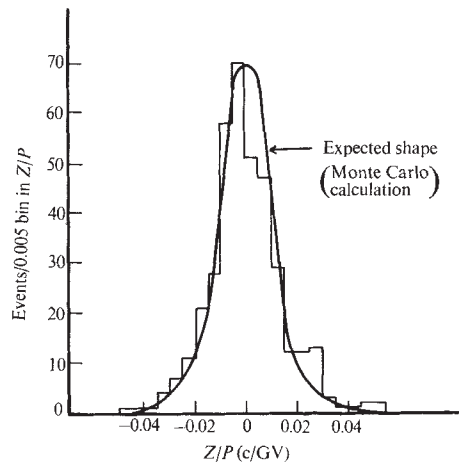


Fig. 3 377 events (second flight) straight-through (magnet off) data fit to curved trajectory.

presents results of previous experiments, all limits shown having 95% confidence level.

Because the antimatter candidates of Table 3 were potentially a greatly enriched sample, we inspected the spark chamber and pulse height records for each event. They all had a normal appearance, except for a single oxygen event which produced an interaction halfway through the last spark chamber and deposited 202 MeV (instead of the usual 124 MeV) in the bottom scintillator. The spark chambers showed that the interaction had at least three prongs at wide angles to the incident trajectory. Such a violent interaction must have fragmented the incident nucleus thoroughly, making it difficult for the event to produce a pulse of normal height in the bottom counter, let alone the abnormally large pulse we saw. The rigidity of this event was 40 GV/c, two standard deviations from a straight trajectory in our apparatus.

Table 3 Antimatter Search Statistics and Monte Carlo Predictions

Data sample	Rigidity range (GV/c)	Observed antimatter candidates	Monte Carlo predicted spillover
Flight 1	$R < 33$	5	2.6
Helium	$33 < R < 100$	7	6
(6,131 events)	$R > 100$	12	11
Flight 2	$R < 33$	0	1
Helium	$33 < R < 100$	0	4
(3,838 events)	$R > 100$	8	7
Flight 1	$R < 33$	0	0.4
Charge $Z \geq 3$	$33 < R < 100$	1	4
(3,152 events)	$R > 100$	5	7
Flight 2	$R < 33$	0	0.2
Charge $Z \geq 3$	$33 < R < 100$	4	9
(10,445 events)	$R > 100$	8	18
All data	$R < 33$	5	4
combined	$33 < R < 100$	12	23
(23,566 events)	$R > 100$	33	43

Common matter might occasionally make up such a large energy deposition in the lower scintillator, through the combined energy deposition of cascade protons (from the struck nucleus) and of inelastically produced mesons. The material of the spark chamber was sufficient to stop any evaporation products from the struck nucleus. Antimatter, of course, would have all of the energy deposition capability of common matter plus that of the extra mesons resulting from plentiful

annihilation processes. To evaluate the relative probabilities of these two processes, we made a Monte Carlo study that included cascade protons¹⁵ from the struck nucleus in the spark chamber (taken to be aluminium), inelastic pion production¹⁶, and the relativistic fragments of the incident nucleus. For the antimatter case, we added extra mesons to take account of annihilation processes. Averaging over all our data we found that an oxygen nucleus could interact in the fourth spark chamber; only 1% of the time could it make as large a pulse as the one we saw in the counter. On the other hand, we found that a 40 GV/c antimatter nucleus could produce as large a pulse 20–50% of the time. The difference between these two numbers (with even greater disparity with our original estimates) led us to make a detailed study of large pulse height probabilities for this event. We found that the chance of common matter producing the large pulse height is an increasing function of incident rigidity. Furthermore, only high-rigidity events could appear because of the optical distortions of our spectrometer as antimatter. Integrating over our known rigidity spectrum, we found that the chances were about 12% that this oxygen event was high-energy common matter that appeared as antimatter in the spectrometer because of optical distortion and made up the large pulse height by producing many inelastic mesons. Therefore, it finally appears only an insignificant three times easier to explain this event as true antimatter than it does as common matter spillover.

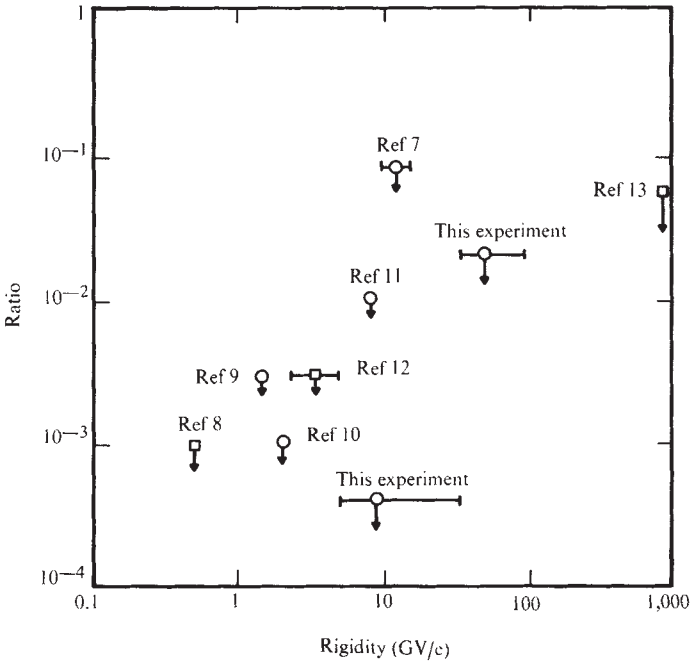


Fig. 4 Summary of present information on upper limits for antiparticles in the cosmic rays at 95% confidence limits. □, $\bar{P}/P$ ratio; ○, $\bar{A}/A$ ratio.

The limits set on antimatter flux by our experiment are considerably lower than for any previous experiment. We consider that we have done as well as possible in the search for antimatter events among helium with our present equipment, because of the contributions to antimatter candidates from nuclear scattering within the detector. A new apparatus, with much less material in the detector, could perhaps carry the helium search further. For a magnetic field integral of 3 kG m, however, the momentum transfer necessary to scatter a common matter event to negative curvature is greater than 90 Z MeV/c. As we noted before, total momentum transfer greater than 300 MeV/c is likely to fragment an incident nucleus. Therefore, on the higher charged elements, nuclear scattering becomes unimportant

and our experiment is limited only by the statistics and by errors in optical reconstruction. We are planning to fly a second-generation magnetic spectrometer with improved optics, which will also have a thick Čerenkov counter following the momentum measurement. Antimatter candidates should interact in this counter about 50% of the time, and the Čerenkov threshold will diminish the response of the counter to the troublesome nonrelativistic cascade products which characterize interactions of common matter. With this innovation and multiple balloon flights, it should be possible to push the upper limit down by another decade or so, or hopefully to make the first positive unambiguous identification of complex anti-nuclei in the primary cosmic rays.

We thank the National Center for Atmospheric Research balloon launch crew at Palestine, Texas, for hospitality. We also thank Dr Charles Orth for help with the Monte Carlo program and Dr John Naugle, who called our attention to the possibility that our very small sample of very high-energy ordinary matter events had to be considered seriously as a cause for the one apparent anti-oxygen event. This work was supported by a NASA contract.

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Molecular Basis of a Mutational Hot Spot in the Lysozyme Gene of Bacteriophage T4

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Investigation of reversion rates and sequencing of amino-acids has shown that one mutational hot spot in bacteriophage T4 is probably a sequence of six identical bases.

It has been known for a long time that mutation frequencies differ greatly at different sites within a gene¹, but the reasons for these differences are not well understood. Here we de-

scribe a frame shift mutation² in the lysozyme gene³ of bacteriophage T4 which reverts with an unusually high frequency, and describe the likely base sequence at the mutant site. We believe that the high reversion frequency of this mutant is due to the presence of six identical base pairs. Previously³ we proposed a model for the origin of frame shift mutations. In general we believe that such mutations are likely to occur in regions with repeating bases or base doublets. The results presented here are compatible with that model and in fact, together with other results, motivated that model.

Reversion Frequency of *e*JD11

The mutation *e*JD11 arose originally in the mutant strain *e*JD10⁴ giving rise to the pseudowild double mutant strain *e*JD10*e*JD11. The mutant *e*JD11 was isolated from the pro-

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geny of a cross of *eJD10eJD11* to *e⁺* (wild type). Crosses of *eJD11* to *eJD10* gave rise to pseudowild double mutant recombinants as well as to *e⁺* phage.

Table 1 Frequency of Revertants

Mutant strain	Frequency of <i>e⁺</i> -like revertants* after one cycle of selective growth† of mutant
<i>eJD11</i>	1.6×10^{-4} , 1.2×10^{-4} ‡
<i>eJ42</i>	6×10^{-7}
<i>eJ17</i>	$< 10^{-8}$

* To determine the titre of *e⁺*-like phage, an aliquot of the lysate obtained after one cycle of selective growth† was added to *Escherichia coli* B grown to about 2×10^8 ml.⁻¹ in broth ('Difco' bacto-tryptone, 10 g; NaCl, 5 g; H₂O, 1 l.) and the mixture was incubated for about 8 min at 37° C. After this period of time for adsorption, five volumes of melted top agar ('Difco'-agar, 7 g; broth, 1 l.) at 45° C were added and 3 ml. aliquots of the mixture were plated on bottom agar ('Difco'-agar, 11 g; broth, 1 l.) in glass Petri plates. After 20 min at room temperature the plates were incubated at 43° C for 4 h and then at 37° C for 2 h. The plates were inverted, 1 ml. of CHCl₃ was poured into the lid of each plate and the plates were examined after 6–12 h at room temperature. Control plates were prepared in a similar fashion with *e⁺* phage. More than 90% of the plaques on the control plates exhibited haloes that were 7–8 mm in diameter. Plaques with haloes greater in diameter than 7 mm on the experimental plates were classified as *e⁺*-like.

† *E. coli* B were grown to a concentration of 10^8 ml.⁻¹ in broth supplemented by 0.1 volume of buffer (Na₂HPO₄, 3 g; KH₂PO₄, 1.5 g; NaCl, 4 g; K₂SO₄, 5 g; H₂O, 1 l.; 1 M MgSO₄, 1 ml.; 1% gelatin, 10 ml.; 0.25 M CaCl₂, 0.4 ml.) and were centrifuged in the cold, resuspended in buffered broth and adjusted to a concentration of 4×10^8 ml.⁻¹. The bacteria were then brought to 37° C and aerated and were infected with a multiplicity of about five phage per bacterium. Two and a half minutes after infection antiphage serum ($k=15$) was added and the culture was diluted 1:4 in broth. At 22 min after infection, 0.1 volume of chloroform was added and the bacteria (in the aqueous phase) were chilled and sedimented in the cold by centrifugation. The bacteria were washed twice with broth and were resuspended in broth. Chloroform was again added followed by 10 µg ml.⁻¹ of egg-white lysozyme. The bacterial debris was sedimented by centrifugation and the lysate was filtered through 'Celite' (Johns-Manville and Co.), centrifuged in the cold at about 20,000g for 70 min and the phage in the pellet were resuspended by incubation overnight in the cold with buffer. The titre of total phage was determined by adsorbing to *E. coli* B as described above for *e⁺* phage and plating on citrate bottom agar ('Difco'-noble agar, 11 g; broth, 1 l.; supplemented after autoclaving with: Tris(hydroxymethyl) aminomethane (1.0 M, pH 8.0), 50 ml.; sodium citrate 2H₂O (25% solution), 10.0 ml.) with citrate top agar (same as citrate bottom agar except with 7.0 gm 'Difco'-agar) supplemented with egg-white lysozyme (500 µg egg-white lysozyme per 2.5 ml. top agar added just before plating). Plaques were counted after overnight incubation at 37° C.

‡ Values derived from independently prepared cultures.

On plating stocks of *eJD11* in restrictive conditions (bottom agar plates (Table 1) incubated at 43°), generally more than 10^{-3} wild type plaques were observed. Wild type phage are known to have an advantage over mutants during the phage growth that occurs in the course of stock preparation, and thus the high frequency of revertants in these stocks is not an accurate index of the reversion frequency.

To obtain a more accurate measure of the frequency of revertants in a single cycle of growth, stocks were subjected to a selective procedure that efficiently eliminates pre-existing revertants: a culture of bacteria infected with mutant phage is exposed to chloroform, a procedure that causes the lysis of bacteria in which a sufficient concentration of lysozyme is present. Anti-phage serum is also added to the culture. Thus bacteria infected with wild type phage are lysed, liberating phage that become inactivated by antiserum; bacteria that contain predominantly mutant phage are not lysed. The unlysed bacteria are sedimented by centrifugation, resuspended, and then lysed by the addition of egg-white lysozyme. The frequency of revertants for *eJD11* treated in this way is given in Table 1. Also included in this table, for the sake of com-

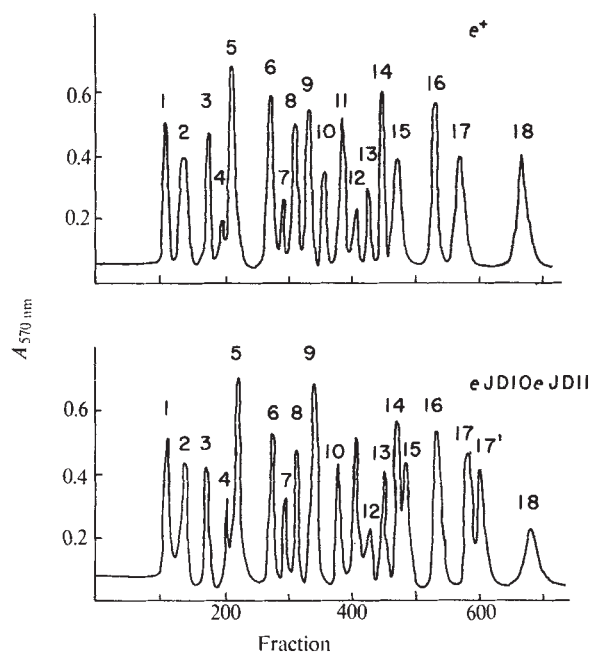


Fig. 1 Elution patterns of tryptic digests of *e⁺* and *eJD10eJD11* lysozyme. Tryptic digests of lysozyme oxidized by performic acid were applied to 'Dowex 50' columns (0.9 cm × 150 cm) and eluted by a gradient of pyridine acetate buffer of increasing pH and pyridine concentration by means of an eight-chamber Varigrad apparatus; fractions of 4.0 ml. were collected and portions from alternate tubes were hydrolysed with alkali and treated with ninhydrin and the absorbance at 570 nm was measured as described previously⁷.

Table 2 Crosses to Determine whether Reversion is at the Site of the *eJD11* Mutation

Cross and control infections*	Frequency of phage that produce plaques that appear mutant †	Maximum No. of base pairs possible between known sites of mutation
Revertant No. 1 × <i>e⁺</i>	4.3×10^{-6}	
Revertant No. 2 × <i>e⁺</i>	2.0×10^{-5}	
Revertant No. 3 × <i>e⁺</i>	1.5×10^{-5}	
Revertant No. 1	1.5×10^{-5}	
Revertant No. 2	1.3×10^{-5}	
Revertant No. 3	1.5×10^{-5}	
<i>e⁺</i>	4.0×10^{-6}	
<i>eJD16eJD12</i> ‡ × <i>e⁺</i>	3.5×10^{-3} , 2.0×10^{-3} §	14
<i>eJD10eJD11</i> ‡ × <i>e⁺</i>	3.0×10^{-3}	12
<i>eJ42eJ44</i> ‡ × <i>e⁺</i>	8.0×10^{-3}	20

* *E. coli* B phr⁻ were grown in broth at 37° C to a concentration of 10^8 ml.⁻¹, chilled, sedimented by centrifugation, resuspended in cold broth and adjusted to a concentration of 2×10^8 ml.⁻¹. 0.1 ml. aliquots of the concentrated bacteria in 16 mm tubes were infected at 37° C with a multiplicity of five of each of the parental phages per bacterium; 9 min later the infected bacteria were diluted 1:10² in cold buffer and were irradiated in the cold with a dose of ultraviolet light equivalent to twenty-five phage-lethal hits. The irradiated bacteria were diluted in broth, and after 90 min at 37° C were lysed by the addition of 0.1 volume of chloroform.

Control infections were performed in the same way except that a multiplicity of ten phage particles per bacterium was used.

† In order to measure low frequencies of mutant phage, lysates of crosses and control infections were subjected to selective growth (for the elimination of *e⁺* or pseudowild phage) exactly as described in Table 1 except that the infection was with about one phage particle per 10³ bacteria. The titre of mutants in the lysate was calculated from a comparison of the titre of mutants recovered after selective growth with that observed after selective growth of known mixtures of *e⁺* and mutant phage.

‡ These strains are pseudowild.

§ Values derived from independently prepared cultures.

parison, are frequencies of revertants in stocks of *eJ42* and *eJ17* similarly treated; these two strains had the highest and lowest reversion frequencies respectively of eleven lysozyme frame shift mutants for which base sequences have been proposed. Thus the frequency of reverse mutation at the *eJD11* site is more than one hundred times greater than that at any other site yet examined.

The revertants of *eJD11* that were observed seemed identical to *e⁺* phage in every respect. They gave rise to plaques under restrictive conditions, and the haloes that were produced around the plaques after exposure to chloroform vapours³ were identical to those of *e⁺* at temperatures ranging from 30° to 43° C. To determine whether the reversion occurred at the site of the original (*eJD11*) mutation, three revertants of independent origin were crossed to *e⁺* phage, ultraviolet irradiation being used to enhance the recombination frequency. If the revertants had been pseudowild, containing the original mutation

Table 3 Frequency of Revertants in Stocks of *eJD10eJD11*

Strain	Frequency of phage that produce plaques that appear mutant †
<i>eJD10eJD11</i> *	1.7×10^{-4} , 1.1×10^{-4} , 1.6×10^{-4} ‡
<i>eJ42eJ44</i> *	1.1×10^{-5} , 2.5×10^{-6}
<i>e⁺</i>	6.5×10^{-6} , 4.2×10^{-6}

* These strains are pseudowild.

† These frequencies were measured as described in Table 2.

‡ Values derived from independently prepared cultures.

Fig. 2 Amino-acid sequence differences between *e* and *eJD10eJD11* lysozymes.

<i>e⁺</i>	
Thr-Ile-Gly-Ile-Gly-His-Leu-Leu-Thr-Lys	Ser-Pro-Ser-Leu-Asn-Ala-Ala-Lys
Peak 18	Peak 10
Thr(Ile,Gly,Ile,Gly)His-Leu-Leu-Gln-Lys	Ser-Pro-Ser-Leu-Asn-Ala-Ala-Lys
Peak 17'	Peak 10
<i>eJD10eJD11</i>	

eJD11 and a second mutation at another site, mutant phage would have been recovered among the progeny of the cross. As Table 2 shows, no mutant recombinants were observed. For comparison, mutant frequencies from control crosses of known pseudowild double mutants to *e⁺* phage are included in Table 2.

Even though the selective procedure described above eliminates pre-existing revertants it seemed possible that a high reversion frequency was only apparent: wild type revertants might, for instance, occur on the Petri plate after plating and produce apparently normal plaques. In fact, in the experiment

Table 4 Mapping of Revertants							
Parent strain	No. of mutants tested	No. of mutants in each map region					
		1	2	3	4	5	6
<i>eJD10eJD11</i>	16						14
<i>eJ42eJ44</i>	11	0	0	1	7	3	0
<i>e⁺</i>	17	0	1	0	9	7	0

Mutant phage were picked from the parent pseudowild and *e⁺* strains described in Table 3. In each case mutants were isolated from two independent cultures. The mutants from *eJ42eJ44* and *e⁺* were mapped by spot-test crosses to a set of overlapping deletions which define six map regions⁵. The mutants from *eJD10eJD11* were crossed by use of spot-tests to *eJD10* (which is in map region 2). Spot-test crosses were performed as follows: 1×10^7 phage particles of each deletion mutant strain and *eJD10* were plated with *E. coli* B and top agar on separate plates containing bottom agar. After 20 min, a small drop (containing about 0.005 ml. of phage at a concentration of 1×10^8 ml.⁻¹) of each of the mutants to be tested was deposited on each plate. After the spots had dried, the plates were incubated at 43° C. Control plates were also prepared, with spotted phage but no test strains on the plates. After overnight incubation, the spots on the control plates were compared with those on the test plates. In most cases the control spots contained no plaques or very few plaques. Recombination was inferred when test spots were clear or contained many more plaques than the control spot.

described in Table 1, a high frequency of small plaques with small haloes was observed; such plaques contain *e⁺* phage and are interpreted as being due to revertants arising during the course of phage growth on the plate. The frequency of reversion (from *eJD11* to *eJD11⁺*) was therefore measured in

the strain *eJD10eJD11*: in this case the double mutant produces plaques under restrictive conditions (it is pseudowild) whereas phage which have reverted at the *eJD11* site contain only the single mutation *eJD10*, and make plaques only on media supplemented with egg-white lysozyme. As shown in Table 3 the frequency of mutants (due to reversion of *eJD11*, as shown below) observed under these conditions is high, and similar to the reversion frequency observed more directly, described in Table 1.

In order to demonstrate that the mutants arising in the strain *eJD10eJD11* were in fact the revertant single mutant

Table 5 Sequence of Amino-acids of Peptide 17' from *eJD10eJD11* Lysozyme

Methods	Amino-acid composition of recovered material							Amino-acid sequence deduced
	Thr	Ile	Gly	His	Leu	Glu	Lys	
Acid hydrolysis	1.2	1.7	2.0	0.7	1.8	1.1	1.0	
Edman degradation, Step 1	0.4	1.7	2.0	0.6	1.9	1.3	N.D.	Thr(Ile,Gly,Ile,Gly,His,Leu,Leu,Glx,Lys)
Carboxypeptidase B *							0.8	Thr(Ile,Gly,Ile,Gly,His,Leu,Leu,Glx)Lys
Carboxypeptidase A + B *				0.2	1.8	1.1 †	1.1	Thr(Ile,Gly,Ile,Gly)His(Leu,Leu,Gln)Lys
Chymotrypsin + carboxypeptidase A *				0.2	1.7	0.1	0.1	Thr(Ile,Gly,Ile,Gly)His-Leu-Leu-Gln-Lys ‡

N.D., not determined.

* Molar recovery of liberated amino-acids.

† Glutamine.

‡ The residues within parentheses are ordered to correspond with the known sequence of the peak 18 peptide of *e⁺* lysozyme⁸.

eJD10 rather than triple mutants involving new mutations at other sites, a number of the mutants were crossed to *eJD10*: in crosses of the putative triple mutant strain some pseudowild *eJD10eJD11* recombinants would be recovered while crosses of a revertant (*eJD10*) strain would yield no recombinants. Table 4 illustrates the results of these and some further control experiments: most of the mutants are in fact *eJD10* and hence revertants at the *eJD11* site. This result is particularly noteworthy because it demonstrates directly that the frequency of reversion at the *eJD11* site is considerably higher than the total forward mutation frequency summed over all other sites within the lysozyme gene.

Amino-acid Sequences

Lysozyme produced in bacteria infected with *eJD10eJD11* phage was purified as described previously⁶, and peptides obtained on tryptic digestion of this lysozyme, as well as *e*⁺ lysozyme, were separated by chromatography on 'Dowex-50'⁷. The only differences observed in the two chromatographic patterns (Fig. 1) are the presence of peak 17' and the smaller size of peak 18 in the tryptic digest of *eJD10eJD11*.

The amino-acid sequence of the peptide isolated from peak 17' is Thr-(Ile,Gly,Ile,Gly)-His-Leu-Leu-Gln-Lys (Table 5). Thus the amino-acid sequence of the tryptic peptide isolated from peak 17' appears identical to that of a tryptic peptide isolated from the triple mutant pseudowild strain *eJD10eJ17eJ42* and described previously⁴.

The sequences of the wild type lysozyme peptides have been established previously and the peak 18 (=T5-II⁸, a product of cleavage by chymotrypsin activity contained in the trypsin preparation) and peak 10 (=T6⁸) peptides have been shown to occupy adjacent positions on the polypeptide chain⁹. Thus the difference in amino-acid sequence between the *e*⁺ and *eJD10eJD11* strains is as seen in Fig. 2.

The amino-acid sequences described in Fig. 2 are compatible with the base sequences of Fig. 3, using codon assignments proposed by Nirenberg¹⁰ and Khorana¹¹.

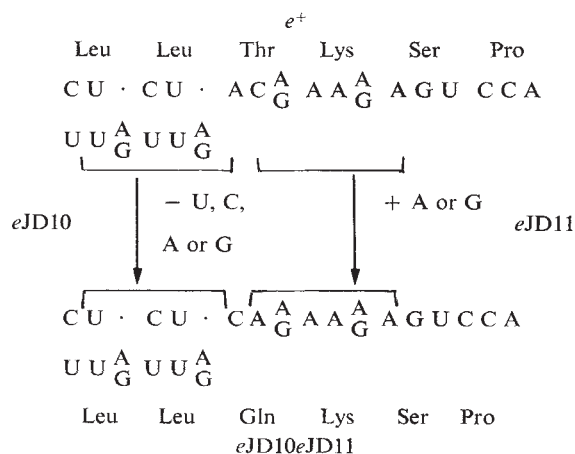


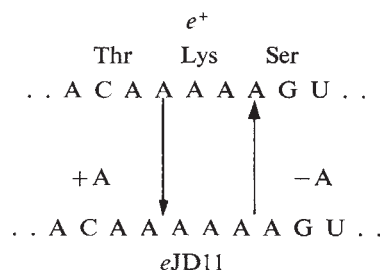
Fig. 3 Base sequences compatible with amino-acid sequences described in Fig. 2.

Earlier analyses of the triple mutant strain *eJD10eJ17eJ42* were compatible only with the assignment of the single base deletions indicated here for the mutation *eJD10*⁴. Thus the mutation *eJD11* must consist of the addition of either A or G as shown above. The Ser and Pro codons were identified unambiguously earlier⁷.

Molecular Basis of Hot Spot

Of fifteen codons cited by Okada *et al.*¹² which have been identified in *e*⁺ lysozyme, fourteen ended in A or U and only

one in C (disregarding the codons for Trp and Met). Therefore the most likely codons for Thr and Lys in the above base sequence of the *e*⁺ strain are ACA and AAA respectively. A likely interpretation for the mutation *e*⁺ to *eJD11*, and for the reverse mutation, is thus as follows:



The high frequency of the reverse mutation (from *eJD11* to *e*⁺) would then be due to a sequence of six consecutive identical base pairs in the DNA.

We have not yet examined the amino-acid sequence of a revertant of *eJD11* to confirm that it is identical to the *e*⁺ strain. As described above, however, the revertants appear identical to *e*⁺ as judged by sensitive physiological and genetic tests.

One of us has subsequently found five different sites in the lysozyme gene at which mutations with high reversion frequencies occur. These five sites are all best interpreted as sequences of five identical base pairs⁵.

As discussed above, stretches of five or more GC base pairs are very unlikely to exist in the DNA of bacteriophage T4 and mutation frequencies in such stretches cannot be measured directly at present. One of us has shown, however, that mutations which revert with very high frequencies are not found in stretches that most likely consist of alternating or random sequences of five or more adjacent A and T residues⁵. Thus we believe that the high mutation frequency described above is due to the presence of a sequence of identical bases, rather than being due to a region rich in AT residues.

We thank D. Thomas and T. Warner for help in the preparation of lysozyme samples and Dr J. Crasemann for permitting us to report her measurements of the reversion frequencies of *eJ17*, *eJ42* and *eJD11*. This study was supported by grants from the Jane Coffin Memorial Fund for Medical Research to Y. O. and A. T., by a grant from the US National Science Foundation to G. S. and by a grant from the US National Institutes of Health to A. T.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Symmetry of Flashes during the Jovian Occultation of β Scorpii

WHEN Jupiter occulted the bright star β Scorpii A on May 13, 1971, a number of spectacular flashes accompanied the fading and brightening of the star as it passed behind the planet's disk and was observed through the Jovian atmosphere. Filmed observations show that the flashes at the time of the disappearance are time-symmetric with those during the reappearance.

disappearance, in the upper part of Fig. 1a; the flashes show up as spikes. The camera was started at UT 18 h 38 m 30 s and the first frame is thought to correspond to that time. The film apparently only records the bright flashes, because some visual observers could still see the star when it was not detected by the film². The filming of the reappearance started at UT 19 h 45 m 30 s but it is not possible to identify the first frame accurately. One bright flash occurred just before the camera was started. The light curve is shown, with the axes reversed, in the lower part of Fig. 1. It can be seen that there is an obvious correlation between the flashes—the two sets are time-symmetric. This correlation was discovered only after the reductions were completed.

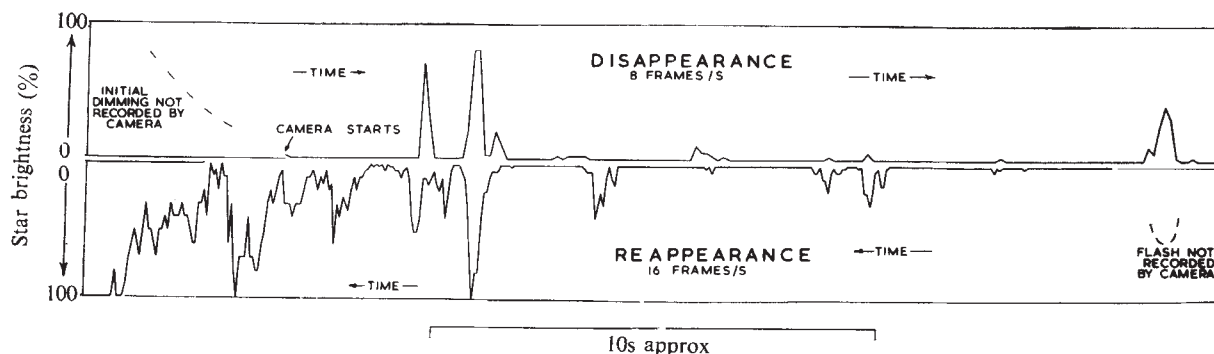


Fig. 1 Light curve of β Scorpii A during occultation by Jupiter.

The observations were made as a class project for the 1971 undergraduate course in astronomy at the University of Cape Town¹. A standard 8 mm cine camera was mounted against the "visitors" eyepiece of the 40-inch telescope at the Royal Observatory, Cape. Preparations were made in the few days preceding the event. The only locally available standard 8 mm film was Kodachrome II and the processing delay excluded any exposure test beforehand. The disappearance of β Scorpii A was photographed at eight frames per second. Because at this speed the camera could run continuously for only 4 min, it was started approximately 1.5 min before the predicted time of disappearance. This was just too late to record the initial dimming of the star. The film of the reappearance, photographed at sixteen frames per second, is more complete, although an early bright flash (seen by visual observers) was missed. The duration of the flashes is generally greater than the interval between frames, the exposure time for individual frames being of the order of 1/60 s. Regrettably there are no time calibrations, other than approximate starting times, to the films.

I have made reductions of the cine film. The film was cut into short lengths, mounted between glass plates, and examined under high magnification using a conventional measuring machine. Because of variations in seeing, the appearance of the star's image fluctuates considerably from frame to frame. There is also interference of the planet's limb, so that it is not possible to make absolute measurements of the star's brightness. But it is possible to make reasonable eye estimates—on an arbitrary brightness scale. These are shown, for the

The flashes are presumably produced by total internal reflexion between atmospheric layers. Thus these observations imply global stratification, rather than local effects, in the Jovian atmosphere. This was also found by the Texas observers³ from their analysis of the gradual dimming and brightening—not the flashes—of the star. It is hoped that these new results can be used in a theoretical analysis.

On a number of frames, when β Scorpii A appeared against the planet's limb, its image was elongated or even split into two components. There was a preferential angle of orientation (north-west-south-east) and a preferred brighter and fainter component. The angle coincides with the known position angle of this visual double³ whose separation is 0.5 arc s. But the cine film suggests that the fainter component is considerably brighter than previously determined.

I thank Mr G. A. Harding, then officer-in-charge of the Royal Observatory, for permission to use the 40-inch telescope. The project was suggested by G. M. Mansfield.

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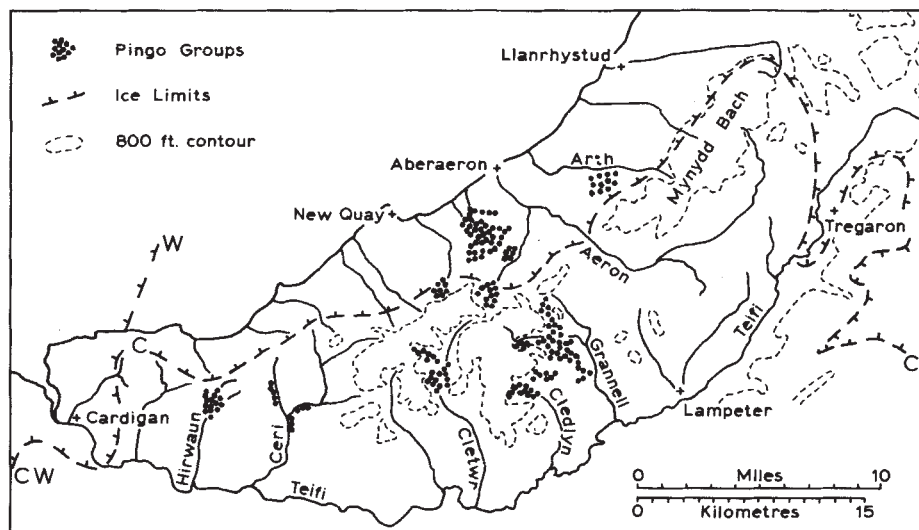
Pingos of Cardiganshire and the Latest Ice Limit

THE first attempt¹ to define the extent of the most recent glaciation in South-West Wales, the "Newer Drift limit", has been disputed by authors²⁻⁴ who place it further north, leaving Cardiganshire almost or quite ice-free. More recently, since the availability of radiocarbon dating, a latest glacial advance almost to the shore of the Bristol Channel has been postulated⁵. The distribution of pingos in Cardiganshire (Fig. 1) may contribute to a resolution of this disagreement.

in East Wales⁷. These examples are on sloping ground. The same holds for the Cledlyn group, where in plan, one quarter to three quarters of the original rampart survives on hill slopes exceeding 2°. Since the pingo with "a segment of the crater rim" remaining is typical of those "in a very advanced stage of decay" in an area of active open system pingos (central Alaska)⁸, it may be taken that ramparts consistently interrupted on the upslope side are indicative of open system pingos.

Four pingo basins in the Cledlyn group, which have ramparts on the downslope side only, have been profiled parallel to the hillslope by augering. All show an asymmetrical profile with

Fig. 1 Distribution of pingos in Cardiganshire. None is known north of Llanrhystud. Ice limits of last glaciation; CC, southern limit of the "New Drift" (after Charlesworth); WW, southern and eastern limit of the "Irish Sea Ice" (after Wirtz).



A pingo is an ice-cored mound formed in the permafrost. When the ice lens melts, it leaves a basin surrounded by a rampart. Open-system pingos, to which those of Cardiganshire belonged, are fed by water under pressure, coming from the unfrozen strata beneath the permafrost. These tend to form in the same locality over a period of time so that the final remains may consist of intersecting ramparts from which it is difficult to reconstruct individual pingos. In the best preserved examples such as those in the upper Cledlyn basin⁶, the ramparts themselves are distinctive. They tend to be of relatively constant width and height for most of their length, and where they die out they taper gradually and their crest falls gradually. Rampart-like ridges may be found between close-set kettle holes but they are very localized, and they lack the level, nearly horizontal crestline of the pingo ramparts. The upslope sector of the rampart is frequently missing in the pingos near Llangurig

the deepest part of the basin close to the surviving part of the rampart (Fig. 2a). Three pingos in the same group, sited on the valley bottom (slope 1°-2°), with ramparts surviving all around the basin, have a fairly symmetrical profile (Fig. 2b). It is suggested that where the upslope part of the rampart is missing it has collapsed into the basin⁹.

The pingo basins contain a grey clay-silt (with >90%, often 96% to 98%, of the fine fraction >0.02 mm). The basins vary greatly in depth, but in the deepest (Fig. 2a) the thickness of the clay-silt exceeds 9.3 m. Its base was not reached at 11.77 m and 10.15 m below the bog surface in *a* and *b*, respectively, of Fig. 2. Overlying this pond mud is an unbroken sequence of organic sediments and peat. In the Llangurig pingos the junction of a similar grey mud-organic succession has been dated to Pollen Zone III/IV (ref. 10) and in the Ardennes a similar age has been established¹¹. The regular,

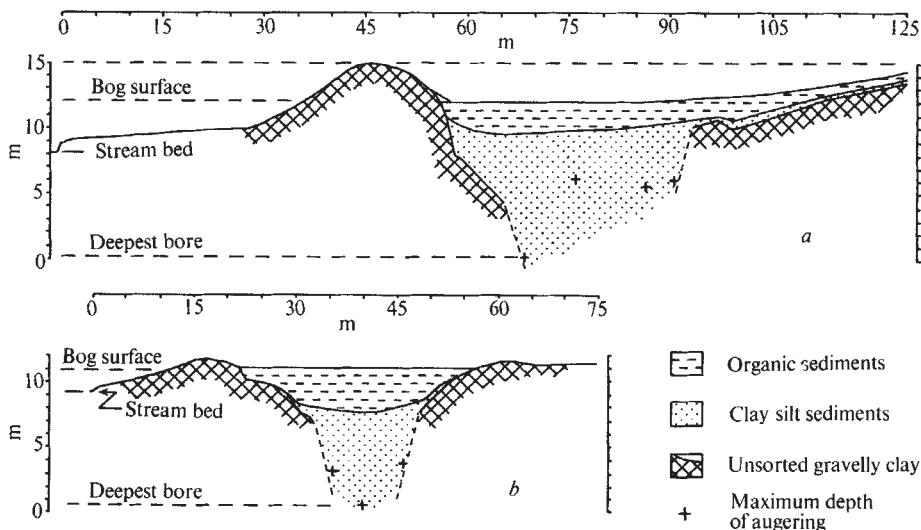


Fig. 2 Profiles of two pingos of the Cledlyn group, South Cardiganshire. The vertical scale is twice the horizontal. Continuous subsurface boundaries are based on contacts determined by augering, broken boundaries by the auger depths shown (+), which give minimum slopes to these boundaries.

undisturbed base of the organic sediments in these cases shows that the pingo ice had already melted out and that the top of the grey clay-silt was stable before the end of Pollen Zone III.

The date of their formation remains open; but the significance of the pingos for the age of the latest deglaciation of Cardiganshire, perhaps, lies more in the necessity for a time gap between deglaciation and the possibility of pingo formation, as is shown by a recent study of the relationship of contemporary pingos to glacial limits in the Yukon¹². In the central and southern Yukon, two glacial limits are indicated by moraines outside the Neoglacial moraines associated with the snouts of modern glaciers. These belong to the McConnell Glaciation, dated by overlying organic silt to >12,000 BP and equated with the Wisconsin, and the Reid Glaciation dated by overlying organic material as >42,900 BP and therefore Early Wisconsin or Pre-Wisconsin in age¹³. Outside the Reid limit there are glacial deposits "lacking distinctive geomorphic form" (ref. 13), and beyond these the unglaciated part of the Yukon Plateau. Hughes¹² found that pingos are most abundant in the unglaciated region and "extend into the areas of Pre-Reid Glaciation without any sharp decrease in density". Density is, however, "markedly lower in areas that were last glaciated during the Reid advance", while "only two definite and two probable pingos have been identified within the limits of the McConnell advance".

Yet present day pingos in Canada and Alaska are believed to have been forming continuously for several thousand years, probably for the past 4,000 yr and just possibly for the past 7,000 yr (ref. 8). Their virtual absence in the considerable area which was covered by the McConnell advance but has been ice-free for more than 7,000 yr makes it clear that the growth of pingos has not followed on the retreat of the ice even in conditions of discontinuous permafrost. Hughes¹² also suggests that the low density of pingos in the areas of the Reid Glaciation may be attributed to the relative freshness of the glacial drift morphology and materials. For the open system pingos of the Yukon basin are mostly sited on slope deposits, "on slopes mantled by several hundred feet of slope wash sediments and colluvial rock debris" (ref. 12). In central Alaska, "none have been found on glacial drift" (ref. 8).

The evidence of the present day open system pingos of central Yukon suggests that rare examples may occur inside the limit of the last glaciation, but that high densities are found only outside it. The pingos of Cardiganshire are not sparse in distribution but occur in a number of localities where they are found in considerable profusion suggesting that several generations have developed. These pingo groups are sited in open valleys or basins where the long regular slopes indicate that slope processes have been long dominant. The frequent worn and rounded pebbles of local rock in the slope deposits east of the Ceri basin (Fig. 1), and the northern erratic pebbles and Irish Sea Till material in the Ceri and Hirwaun basins, show that these slope processes have transformed a landscape of glacial deposition. The pingos involve these slope deposits.

Charlesworth believed that the sand and gravel deposits around the Teifi estuary and those of the upper Teifi below Tregaron marked the ice limit of the last glaciation and drew a line between them, passing around the northern end of the Mynydd Bach (Fig. 1). To the south of the Aeron, this was based on limited evidence for ice margin drainage, but north of this the evidence was "singularly scanty" and he described his line as "conjectural" (ref. 2). Wirtz interpreted the evidence around the Teifi estuary and further south-west as indicating the limit of the Irish Sea Ice of the last glaciation, the area to the east and north-east being ice free². This seems more in accord with the distribution of pingos which are well developed both inside and outside Charlesworth's "Newer Drift" limit.

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Palaeomagnetism and the Origin of the Grenville Front

THE Grenville Province is bounded on the north by the Grenville Front (Fig. 1) and on the south-east by the Appalachian Fold Belt. To the south-west in the St Lawrence Lowlands, Grenville rocks pass beneath sub-horizontal Lower Palaeozoic cover rocks. The Grenville Front is observed to be a fault or metamorphic boundary extending for 1,500 km which truncates several older structural trends. It separates Archaean and Lower and Middle Proterozoic rocks (some of which are unmetamorphosed) to the north from more strongly metamorphosed but generally younger rocks to the south.

According to the theory of plate tectonics, there are three types of plate junctures named by the motions that occur across them—divergent, convergent, and strike-slip. The Grenville Front has no large linear belts of basic rocks such as characterize divergent or convergent junctures. Moreover, the metamorphic trends (they are predominantly northerly¹) in the Province generally are not parallel to the Front. Thus plate theory would suggest that the Grenville Front is a strike-slip juncture formed after the main metamorphism of Grenville rocks. In this article, we shall summarize the palaeomagnetic evidence for this idea.

The Grenville Province² consists of (1) basement gneiss complexes; (2) large anorthosite-mangerite plutons; and (3) smaller intrusions of gabbro, diorite, syenite and granite, all

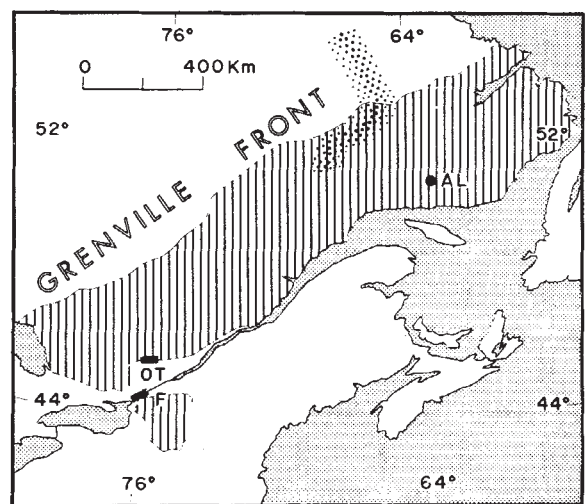


Fig. 1 The Grenville Province is marked by vertical shading. AL is the Allard Lake Anorthosite, OT the Ottawa area basic intrusives, and F the north-west dykes of the Frontenac axis. The dotted area shows the continuation of the Labrador Trough rocks (Lower Proterozoic) into the border zone of the Grenville Province and their clockwise deflexion at the Front.

of which have undergone moderate to high-grade regional metamorphism. Following this intense metamorphism small granite and syenite bodies (4) and basic dykes (5) were emplaced. Elements (1) to (4) yield K-Ar dates with an average of 950 m.y., but older dates, varying from 1,700 to 1,100 m.y., are obtained by the Rb-Sr and U-Pb methods. The basic dykes have a variety of trends and ages. One prominent set (the so-called Grenville dykes³) are late Precambrian (about 675 m.y.); they are probably related to the early rifting stages of the Palaeozoic diastrophic cycle that created the Appalachian Fold Belt and are therefore not considered here.

Early palaeomagnetic studies of element (1) (Russell Border Belt⁴ of the Adirondacks, declination 145, inclination +50), of gabbros⁵ of element (3) (Thanet 093, +62 precision⁶ $k=5$, Tudor 328, +11 $k=5$, and Umfraville 115, +43 $k=8$), and of various rocks (mean direction 287, -44) related to element (3), yielded magnetization directions aligned along east-south-east to west-north-west axis. Both normal and reversed polarities are present, and the scatter of directions is high, but detached demagnetization studies of rocks from three places have recently produced results with much less internal scatter, the first⁷ (from element 2), from the Allard Lake anorthosite of eastern Quebec (AL of Fig. 1, mean direction 297, -79 $k=88$ pole 39S, 140E $A_{95}=18$). The second result (Park and Irving, unpublished) is from six north-west trending basic dykes of the Frontenac axis near Kingston (F of Fig. 1, mean direction 103, +50 $k=112$ pole 12S, 163E $A_{95}=7^\circ$). K-Ar whole-rock¹⁸ and biotite⁹ ages of 751 and 817 m.y. have been reported from these dykes and presumably indicate their minimum age.

A third result from basic intrusions of element (3) in the Ottawa area is now briefly described. Two bodies situated about 50 km west of Ottawa were sampled. One intrusion is near Bryson (45° 41' N, 076° 37' W; five sites) and the other is at Cheneaux Falls on the Ottawa River (45° 35' N, 076° 40' W; one site). In another area, 20 km north of Ottawa in the Gatineau Valley, several small bodies marginal to the Wakefield syenite were sampled (45° 37' N, 075° 51' W; eight sites). All are dioritic or gabbroic in composition and are foliated to varying degrees. At each site five to seven core samples were drilled (seventy in all). Two cylindrical specimens were cut from each core. Detailed alternating field (a.f.) demagnetization studies were made of one specimen from each core and an end-point determined. Thirteen specimens had no stable end-points. For the other fifty-seven

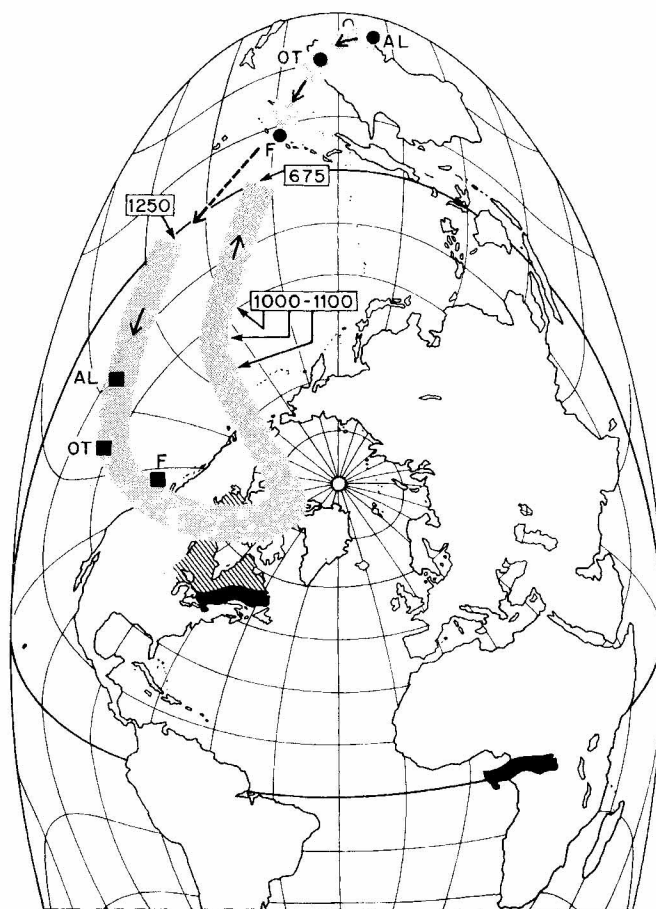


Fig. 2 The polar sequence AL-OT-F is obtained from Grenville rocks (see legend to Fig. 1 and text). The Grenville Province is black. The large loop is the Proterozoic polar path relative to the rest of the Canadian Shield which is shaded. The sense of polar motion in the loop is denoted by arrows and the terminal ages are given in millions of years. This loop was first roughed out by Du Bois¹⁷ and has since been further developed by Spall¹⁸ and by Robertson and Fahrigh¹⁹. The loop drawn here is deeper than that of earlier authors and has been constructed using a recent compilation of Precambrian results (unpublished work). The polar motions depicted are relative to the Canadian Shield only; the continental outlines are added to provide a frame of reference. The proposed position of the Grenville Province (in what is nowadays West Africa) before the formation of the Grenville Front has been obtained graphically by moving the Grenville poles (now plotted as squares) into the descending limb of the loop and moving the Grenville Province accordingly. The uncertainties in this procedure are discussed in the text.

Table 1 Summary of Results

	D, I	N	k	α_{95}
B04	301, -63	4	33	16
B04 (M)	296, -61	6	22	12
B05	269, -59	4	94	10
B11	278, -69	5	47	11
B (Ave)	286, -64	4	99	09
C13	109, +64	4	14	26
G01	266, -70	7	761	02
G20	104, +59	4	11	29
G19	068, +69	9	9	18
G18 (N)	041, +62	4	57	12
G18 (R)	267, -74	5	633	03
G17	266, -61	5	57	10
G27	070, +67	3	71	15
G26	276, -61	3	17	31
G (Ave)	260, -67	8	65	07
Total	271, -66	13	61	05
Pole	32S, 155E	13	25	08

The B sites are from the Bryson body, B04M being data of Murthy³. The C site is from Cheneaux. The G sites are from the Gatineau Valley. The site numbers are laboratory catalogue numbers and have no geological significance. D, I are declination and inclination, N the number of cores (2 specimens from each) or number of sites in the averages, k is Fisher's precision, and α_{95} the radius of the circle of confidence ($P=0.05$). At one location (G18) two irregular dyke-like bodies have opposite polarity.

specimens stable end-points were found in the field range of 150 to 300 Oe. The second specimen from each core was then demagnetized in this field. Eight sites have reversed and five have normal magnetization (Table 1). The corresponding poles for this and the other Grenville results are situated near Australia (Fig. 2) and fall in a sequence corresponding to their supposed ages—anorthosite (AL element 2), minor plutons (OT element 3), and north-west trending dykes (F element 5).

The path of apparent polar wander relative to the rest of the Canadian Shield for the interval between the Mackenzie¹⁰⁻¹² (1,250 m.y.) and Franklin¹³ (675 m.y.) igneous episodes is also plotted in Fig. 2. This path has the form of a loop on which the Grenville poles do not fall, which could mean that the late Proterozoic polar path is much more complicated than is depicted in Fig. 2. For example, the Grenville poles could represent an early section of the descending limb of the polar loop as indicated by the dashed line. (This is an improbable reconstruction since the dykes of pole F are almost certainly younger than the Mackenzie diorites, the starting point for the polar loop, and the poles from rocks in the age range 1,400-1,300 m.y. fall in the east-central Pacific, not near Australia.) Alternatively, we may suppose that the Grenville Province was

once displaced relative to the remainder of the Canadian shield^{14,15}.

This hypothesis has several interesting consequences. The first is that the magnetizations of the Allard Lake anorthosite and the Ottawa basic rocks were acquired about 1,200 m.y. ago presumably during cooling after the last penetrative metamorphism; that is the magnetizations "see through" the K-Ar event at 950 m.y. The second consequence is that at the time of metamorphism, the Grenville Province was situated many thousands of kilometres distant from the older Canadian Shield, its position relative to the Shield (Fig. 2) being such that motion required to bring them together is predominantly dextral strike-slip. A component of convergence perpendicular to the front may have been present and its magnitude determined by this method depends on where the Grenville poles are placed on the descending limb of the polar loop. Although the data allow considerable freedom, whatever placing is adopted dextral strike-slip predominates, and relative motion is of the order of several thousands of kilometres.

This idea, that the Grenville Front is a strike-slip juncture along which motions comparable in scale with current plate motions occurred, could explain many observed features. It could explain the zones of cataclasis and mylonitization along the front that are believed to have developed during the later stages of deformation, after the main metamorphic episode². It could explain how generally older, sometimes unmetamorphosed rocks to the north have been brought into such close contact with the younger more highly metamorphosed terrain of the Grenville Province. It could explain the presence of a border zone of mixed rocks south of the Front, some of which (notably the extension of the basic rocks and iron formation of the Labrador Trough) swing westward as if they have been rotated clockwise (Fig. 1).

We suggest that the time of collision of the two continental masses is marked by the peak of the polar loop; more specifically that the rapid apparent polar change that occurs in certain Keweenawan rocks whose age is indistinguishable radiometrically¹⁶ actually corresponds to and is caused by this collision. On this view the collision occurred between 1,200 to 1,100 m.y. ago, and the K-Ar dates (average 950 m.y.) then correspond to a period of vertical adjustment (general uplift) consequent on this collision.

Finally, we note that the predominantly strike-slip juncture of the present day Pacific and North American plates has relatively small divergent sections at points where strain is transferred from one strike-slip fault system to another. By analogy we suggest that the Keweenawan Basin and the Naskaupi Fold Belt in Labrador were developed as tensional rifts (basic intrusions and lavas and thick clastic sediments) associated with geometrical irregularities in the developing Grenville Front.

The graphical operations depicted in Fig. 2 were carried out on a large globe (scale 1 cm = 1°) using spherical plastic overlays, accuracies of ¼° being readily attainable. This globe was constructed by John Geuer and Odette Degen.

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BIOLOGICAL SCIENCES

In situ Hybridization of Adenovirus RNA and DNA

THE methods which have been developed for annealing nucleic acids *in situ*^{1,2} have recently been utilized in locating the positions of satellite fractions of DNA in the cells of a number of species including mouse^{3,4} and man⁵. RNA complementary to viral DNA can be used in a similar manner to localize viral nucleic acid in the host cell⁶.

Adenoviruses have been shown to induce chromosome aberrations in both permissive and non-permissive cells⁷⁻⁹, and in the case of the three serotypes highly oncogenic in hamsters¹⁰ to induce non-random chromosome damage to human cells *in vitro*^{11,12}. In this report we describe our initial results using adenovirus type 12 complementary RNA (cRNA) to follow virus replication in human cells and to examine the relationship between the viral genome and the host cell chromosomes.

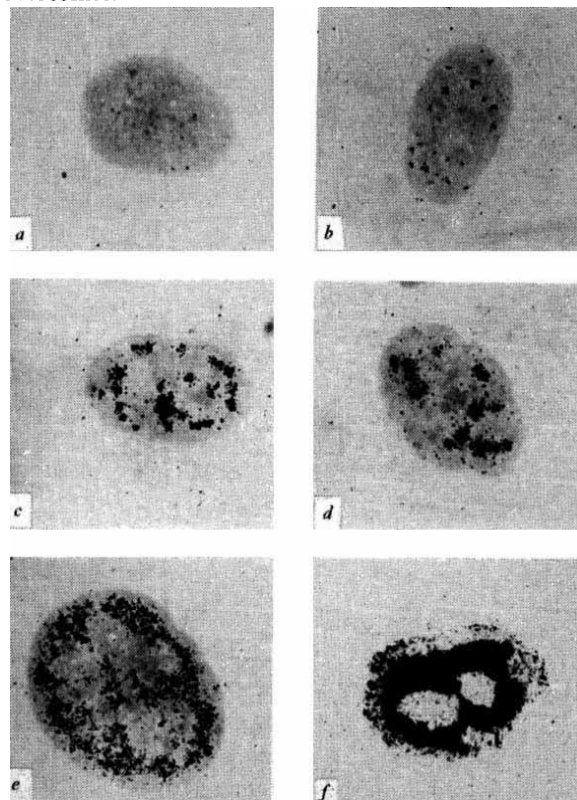


Fig. 1 Autoradiographs of nuclei from HEL cells stained with 'Giemsa' after 8 weeks exposure. a, Uninfected cell; b-f, progressive stages of viral DNA synthesis detected by *in situ* hybridization of adenovirus cRNA ($\times 480$).

Adenovirus type 12 (Huie strain) was passed in human embryonic kidney (HEK) cells. Infected cells were disrupted by ultrasonic treatment, 2 g of caesium chloride added to 4 ml. aliquots of virus/cell extract, and the samples centrifuged to equilibrium in an SW65 rotor in a Beckman L2-65B ultracentrifuge. After three centrifugations in CsCl the virus band was dialysed against frequent changes of 0.01 M Tris (pH 7.2) for 48 h at 4° C.

After a further 3 days at 4° C in 0.01 M Tris, during which time there is a loss of pentons from the virion and a consequent greater susceptibility to disruption¹³, DNA was extracted from purified virions using the method described by Levine and Ginsberg¹⁴. Adenovirus type 12 cRNA synthesis was carried out for 90 min at 37° C in 0.25 ml. of Tris-HCl buffer, pH 7.5 (at 37° C) containing 10 µg of purified viral DNA as template, 4 units of *E. coli* RNA polymerase¹⁷, 0.02 mM each of ATP (Schwartz-Mann 20.7 Ci/mmol), UTP (Amersham TRK 289, 10.5 Ci/mmol), CTP (TRK 339, 20 Ci/mmol) and GTP (TRK 314, 9.9 Ci/mmol); 2.5 mM MnCl₂, 10 mM MgCl₂, 1.6 mM spermidine, 5 mM mercaptoethanol, 6 mM KCl, and 0.48 mM PO₄. The rate of synthesis was roughly linear over the incubation period. After 90 min, RNAase-free DNAase (Worthington) was added (final concentration 40 µg/ml.) and digestion of the template allowed to proceed for 10 min at 37° C. Cold *E. coli* carrier RNA (50 µg) was added and the mixture extracted twice with phenol followed by passage through a 'Sephadex G-50' column equilibrated with 0.1 × SSC (SSC = 0.15 M NaCl–0.015 M sodium citrate). Fractions under the coincident peaks of absorbance (260 nm) and radioactivity were combined and lyophilized. The lyophilizate was then redissolved to give a final concentration of 5 × SSC. The estimated specific activity of the product was 10⁸ d.p.m./µg.

The method used for cell growth, virus infection and preparation of chromosome spreads were as previously described^{9,12}. Air dried preparations of uninfected and virus-infected human embryo lung (HEL) cells fixed with methanol/acetic acid were treated with 0.2 N HCl at room temperature for 20 min, to denature the DNA, followed by washes of 10 s each in 70%, 90%, 95% and absolute alcohol. The slides were dried and 4 µl. of adenovirus cRNA, in 5 × SSC, was applied to each slide which was then sealed with a coverslip, and incubated for 10 h at 65° C.

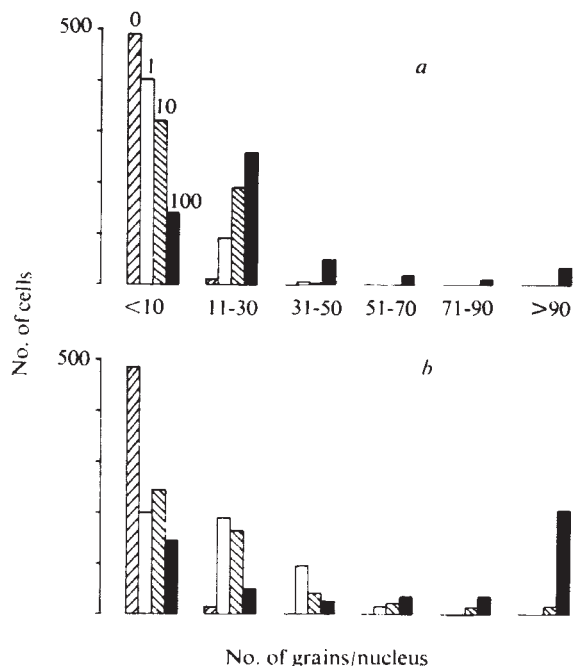


Fig. 2 Distribution of grains over nuclei of uninfected cells and cells infected with adenovirus 12 at different multiplicities of infection. 0, Uninfected; 1, 10, 100 p.f.u. of adenovirus type 12 per cell. 500 cells were examined for each sample at 24 h (a) and 44 h (b) post-infection.

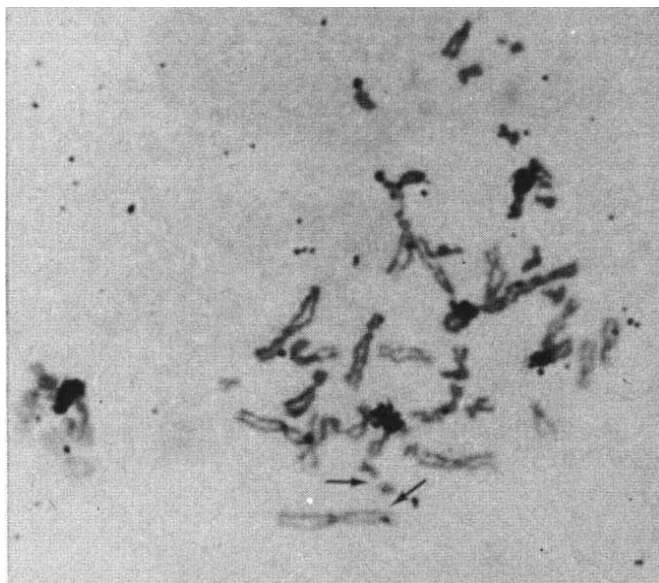


Fig. 3 Metaphase from culture 24 h after infection with adenovirus type 12. Autoradiographic grains in dense clusters indicate sites of hybridization of viral cRNA to synthesized viral DNA in association with chromosomes. Virus-specific damage to chromosomes 1 and 17 can be seen (arrowed).

After removing the coverslips the slides were washed in 2 × SSC, treated with RNAase, 37° C, for 30 min and then washed extensively in 2 × SSC at 4° C. After dehydration in alcohol as previously described, slides were dipped in Ilford K2 emulsion diluted 1–1 with water and stored in lightproof boxes at 4° C. After eight weeks exposure the autoradiographs were developed in Kodak 'D 19B' developer, stained with 'Giemsa' and photographed using a Leitz 'Ortholux' photomicroscope with Ilford 'Pan-F' film.

Autoradiographic grains were located over both chromosomes and interphase nuclei in virus-infected cells with occasional grains in the cytoplasm and with a low background count. The grain count in control uninfected cell preparations was uniformly low.

Interphase nuclei were examined to determine both the distribution of label within nuclei and the total nuclear grain counts. The grain distribution and count over non-dividing nuclei alter with time after infection (Fig. 1) and the numbers of labelled nuclei are clearly related to multiplicity of infection (Fig. 2). In the metaphases from virus-infected cultures the number of grains found was usually low, with a few exceptions (Fig. 3), indicating that in cells reaching mitosis during the 48-h period post-infection there had usually been little or no synthesis of viral DNA. The grain count over chromosomes was, however, increased with higher multiplicity of infection, indicating that the grains seen represented the location of either whole viral genomes or fragments of viral DNA in the preparation. The grains were usually found to be associated with the chromosomes and isochromatid labelling could be found (Fig. 4).

Specific damage induced by the virus to chromosome No. 17 was present in up to 40% of the metaphases, but grains were only rarely found in association with this locus. The distribution of grains over the karyotype was random (Fig. 5) except for preferential labelling of chromosome No. 1. This chromosome also shows virus specific damage but at a lower frequency than chromosome No. 17¹²; the label was not always associated with the sub-terminal site of virus-induced structural damage on this chromosome.

These findings show that the sites of chromosomal damage are not necessarily those which are associated with the sites of major viral DNA accumulation. This tends to confirm the findings from experiments with ³H-thymidine¹¹ uptake that viral DNA synthesis may not be required for the induction of

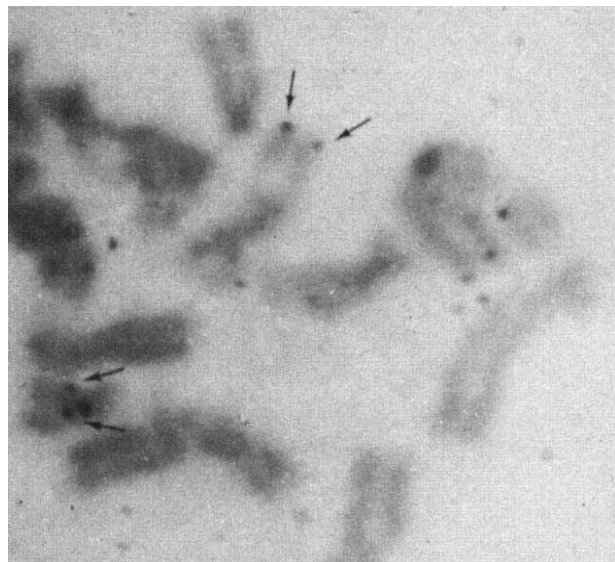


Fig. 4 Autoradiographic grains in association with chromosomes. Isochromatid labelling arrowed.

chromosome aberrations by adenovirus. The results also indicate that there must be few cells capable of undergoing mitosis after massive viral DNA synthesis has occurred. This agrees with the fact that host DNA synthesis becomes repressed during the course of infection of human cells with this virus¹⁵. The isochromatid labelling found in some cells could indicate integration of viral DNA or, at least, preferential localization of virus DNA in association with the host cell genome. It has been suggested that the specific aberration in chromosome No. 17 represents a host cell response to infection with adenovirus type 12, resulting in the synthesis of a host-specified product¹². The damage which is randomly distributed could result from a different mechanism; for example, the DNA-specific endonuclease associated with the penton bases of the virion¹⁶ may affect the host genome in an apparently random manner.

From the calculated specific activity of the input RNA, and assuming a genome size of 2.3×10^7 with an autoradio-

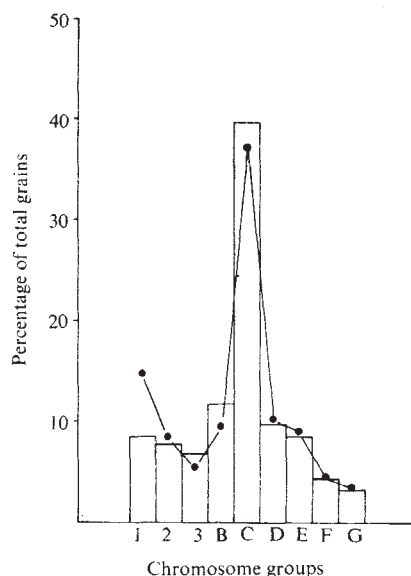


Fig. 5 Percentage distribution of autoradiographic grains over the karyotype. The background histogram is based on the distribution of chromosomal material by length¹⁸. ●, Grain distribution. 100 metaphases were analysed from cultures infected 24 h previously with 100 p.f.u./cell.

graphic efficiency of 10%, we would expect, with about 95% certainty, 2–3 grains per whole genome hybridized after an exposure of about 300 h. This is calculated from an average expectancy of 2–3 grains yield per 100 h of exposure for each whole genome hybridized. The technique of *in situ* hybridization of viral nucleic acids should give valuable information about replication of virus in permissive cells and the fate of the viral genome in neoplastic cells. Further experiments are in progress to examine the relationship between virus and host cell in cells transformed *in vitro* and in cells from induced tumours in animals.

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Effect of Hormonal State on Cell Number and Functional Maturation of the Brain

It is known that thyroid administration interferes with post-natal cell formation¹ and affects the functional maturation of the brain^{2,3}. Glucocorticoids also inhibit cell division in the brain^{4–6}, but the ultimate behavioural consequences of treatment during infancy with thyroid and with adrenocortical hormones seem to be different^{2,7}. In attempting to understand these differences a study was made of the effects of cortisol on postnatal cell formation in the rat brain. Further details are given elsewhere⁸.

Cell number was assessed by DNA determination, which within certain limits gives a fair approximation¹. The cell number in the cerebrum of the newborn was 55% and in the cerebellum 3% of the adult value, which was reached at about 3 weeks after birth (Fig. 1). Cortisol treatment led to a marked

reduction in the normal increase in cell number. During the period of cortisol administration the inhibition was severe, 90% in the cerebrum and 70% in the cerebellum between days 2 and 5; but after treatment had been stopped the rate of increase in cell number was similar to that in the controls. In the 35 day old experimental animals, however, there remained a permanent deficit in cell number amounting to about 20% in the cerebrum and more than 30% in the cerebellum.

To determine whether cortisol affected primarily cell formation or cell destruction the synthesis of ^{14}C -DNA was studied 1 h after the animals received a subcutaneous injection of 2- ^{14}C -thymidine (Fig. 2). During the period of cortisol treatment the formation of ^{14}C -DNA was strongly inhibited; in animals 5 days of age the ^{14}C -DNA content as a percentage of the control values was about 30% in the cerebrum and 50% in the cerebellum. The recovery was considerable and in the brain of 13 day old experimental animals the fraction of the total cell population in replicating phase, which can be estimated by expressing the amount of ^{14}C -DNA formed relative to the total amount of DNA, was similar to that in the controls. A tendency to compensate for the initial cell deficit by accelerated mitotic activity was indicated by a significant increase above the control level in the amount of ^{14}C -DNA both in the cerebrum and in the cerebellum of 20 day old cortisol-treated rats. Nevertheless, rapid cell division ceased at about the same age as in the controls; the labelling of DNA decreased markedly between 13 and 20 days of age, and the total amount of DNA reached the final level at 20 days (Figs. 1 and 2).

The effects of cortisol treatment on the formation of ^{14}C -DNA were not attributable to alterations in the availability of ^{14}C -thymidine in the brain. The concentration of acid-soluble ^{14}C , which was combined chiefly in thymine-containing compounds, was significantly increased in the brain of cortisol-

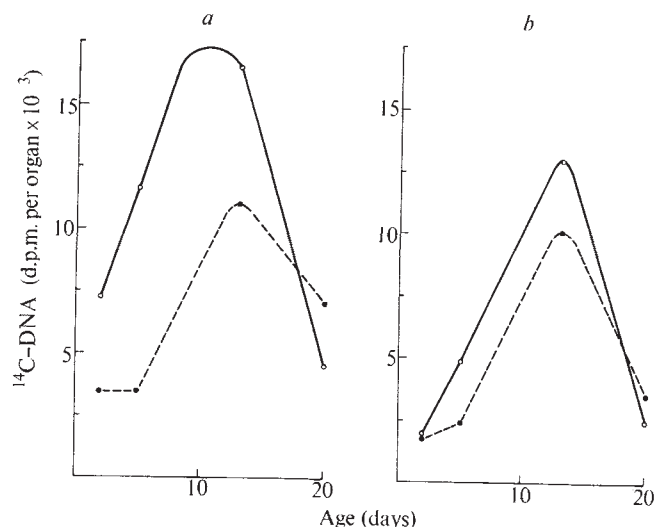


Fig. 2 Effect of cortisol treatment on the synthesis of ^{14}C -DNA in (a) the cerebrum and (b) cerebellum at 1 h after a subcutaneous injection of 2- ^{14}C -thymidine (59 mCi mmol $^{-1}$, Radiochemical Centre, Amersham, Bucks; dose 20 μCi 100 g $^{-1}$ body weight). For experimental treatment and statistical analysis see legend to Fig. 1. The number of observations was fourteen in a and fifteen in b in the experimental and sixteen in the control group. The residual variance ($\times 10^3$) was 354 in the cerebrum and 996 in the cerebellum. The labelling of DNA changed significantly with age in both a and b. The exact period when the differences between control and experimental animals were statistically significant was 2–13 days in the cerebrum and 5–20 days in the cerebellum. $\circ$, Control; $\bullet$, cortisol treated rats.

treated rats during the period of severe inhibition of DNA synthesis, whereas it was slightly reduced at the age of 20 days when the formation of ^{14}C -DNA was above the normal control level.

In spite of the marked influence of cortisol treatment on postnatal cell formation, the age curves for average cell size (DNA concentration) and composition of the cells (RNA/DNA and protein/DNA) were not significantly different from controls⁹. Furthermore, the treatment did not affect significantly the maturation of glucose metabolism in the brain^{6,8}. Thus, it seems that the "biochemical differentiation" of the brain was not adversely affected by exposure to cortisol in infancy.

Table 1 Effects of Treatment with Thyroid and Adrenocortical Hormones on Brain Development

Treatment	Thyroid hormone	Corticosteroids
Postnatal cell formation	Reduced ¹ ; premature termination	Reduced ^{4,5} ; inhibition during the period of treatment (1–5 days after birth)
Appearance of innately organized behaviour	Advanced ^{2,11}	Retarded ¹¹
Performance in tests of adaptive behaviour	Impaired ¹⁰	Normal ⁷

* Present observations.

It was shown previously that treatment of newborn rats with thyroid hormone leads to a deficit in the final cell number of the brain of similar magnitude to that observed in the present work in rats treated with cortisol¹. Treatment with thyroid hormone advances the functional maturation of the brain, as indicated by the appearance of innately organized behaviour, but when the animals grow up, their performance in tests of adaptive behaviour is impaired^{2,10}. Balázs *et al.*¹ proposed that this may be due to the deficit in the final cell number and specifically in microneurons in certain regions of the brain. The effects of cortisol on behaviour are apparently different from those after thyroid treatment (Table 1); the appearance of certain features

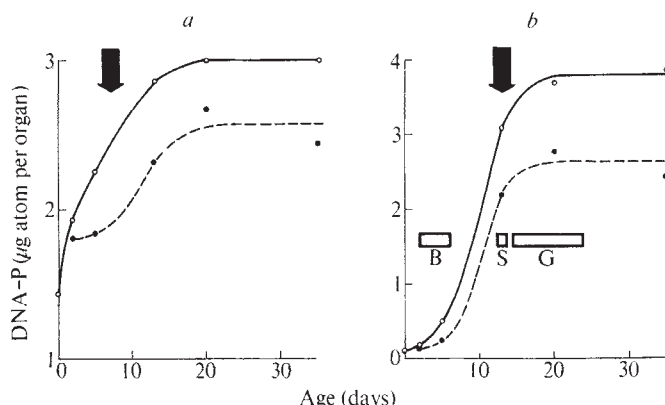


Fig. 1 Effect of cortisol treatment on the total amount of DNA in (a) the cerebrum and (b) the cerebellum of male Porton rats. Treatment—intraperitoneal injection of 0.2 mg cortisol acetate (a gift from Organon) from the first to the fourth day inclusive (day of birth, day 0); littermate controls received the same volume of saline (8 μl). The brains were dissected, and the tissue constituents analysed as previously described¹. The data, except those for the newborn animals which were taken from a previous study¹, were analysed by analysis of variance with a two way classification (experimental or control against age) and the mean values are given; the significance level was set at $P=0.01$ (ref. 19). The total number of observations was nineteen in both the experimental and the control group. The residual variance was 0.0146 in a and 0.0027 in b; the value for the cerebellum refers to the logarithmically transformed individual data ($\times 10$). The DNA content of both the cerebrum and cerebellum changed significantly with age. The exact period when the differences between control and experimental animals were significant was 5–35 days in the cerebrum and 2–35 days in the cerebellum. $\circ$, Control; $\bullet$, cortisol treated rats. The blocks in b indicate the time of the differentiation peak of the postnatally formed neurones in the cerebellar cortex as given by Altman¹³: B, basket cells; S, stellate cells. The period is also indicated when about 50% of the granule cells (G) are formed. The arrows indicate the age when the effect of treatment with thyroid hormones becomes statistically significant¹.

of innately organized behaviour, such as swimming, is retarded¹¹ and there is impairment of motor coordination and emotional control, but the performance of the corticosteroid-treated animals in tests of adaptive behaviour is not impaired⁷. Thus an explanation based simply on reduction in number of microneurons cannot account for the observed effects of hormonal imbalance in early life. It was noted, however, that cell multiplication was inhibited by corticosteroids mainly during the period of treatment, that is days 1–5 after birth (see also refs. 4 and 5), whereas it was affected by thyroid hormone only after a delay of 7–12 days after the start of the treatment, depending on the region of the brain concerned¹. There is a relatively strict chronological order in the formation of the different types of nerve cell in the central nervous system¹²; this also applies to postnatal neurogenesis as shown by observations on the cerebellum (Altman¹³; Fig. 1). Thus it seems that the consequences of an insult will vary according to the type of cell affected, which will depend on the time of interference with cell formation. Besides the cerebellum other parts of the brain, for example the hippocampus, also exhibit relatively extensive neurogenesis after birth¹³. Thus the different behavioural effects produced by corticosteroids and thyroid hormone may depend on their affecting different types of cells in different parts of the brain. This hypothesis may also apply to the behavioural anomalies in other conditions, such as undernutrition^{4,14,15} and amino-acid imbalance¹⁶ which also interfere with cell formation in the brain. Cell formation is also appreciable during the first 18 months after birth in the human brain^{15,17}, and it probably involves microneurons in view of the evidence from other species. Hence it is possible that in man, as in experimental animals, factors affecting neurogenesis in the infant brain may cause later impairment in brain function. There is also evidence that adverse influences during the early postnatal period can affect the functional development of the brain by influencing the differentiation of the nerve cells¹⁸.

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Role of Contractile Microfilaments in the Release of Histamine from Mast Cells

THE release of histamine and other mediators of immediate type anaphylactic reactions from mast cells is triggered by the interaction of antigen with cell-bound antibody. Antigen-induced histamine release and that induced by Compound 48/80 are energy-dependent processes which are depressed by metabolic inhibitors¹ and follow a similar time course^{1–3}. This type of selective release of histamine is inhibited by the potent anti-asthmatic drug disodium cromoglycate (DSCG)⁴, whereas the non-selective release induced by agents such as the detergent 'Triton X-100', which follows a different time course and is not energy dependent, is not blocked by DSCG. It has therefore been postulated^{4,5} that histamine is released from mast cells by two distinct mechanisms: a selective release of amine-containing granules through a process of exocytosis, and a non-selective release of amines and other cellular constituents as a result of lysis of cell membranes.

There is evidence that endocytosis in macrophages is dependent on a system of actomyosin-like contractile microfilaments in the peripheral cytoplasm. All forms of endocytosis (phagocytosis of bacteria, pinocytosis visible under the light microscope and micropinocytosis of colloidal gold) are blocked by cytochalasins, macrolide fungal products that selectively inhibit the activity of contractile microfilaments^{7,8}. Endocytosis in macrophages and polymorphs is not prevented by colchicine, which disperses microtubules, although the directional movements of these cells—which depend on polarity within the cytoplasm—disappear after colchicine treatment. To investigate the possibility that contractile microfilaments also play a role in the exocytosis of pharmacologically-active substances, we have examined the effects of cytochalasins on the release of histamine from mast cells induced by Compound 48/80, and on mast cell degranulation induced by cell-bound antibody and specific antigen.

To do this, mast cells were obtained from peritoneal washings in balanced salt solution from Sprague-Dawley rats (200 g). Cells were washed twice by centrifugation at 230g for 10 min in siliconized tubes, re-suspended at a concentration of 600,000 mast cells per ml. and divided into 0.25 ml. aliquots in siliconized tubes at 20° C, pH 7.0, for experimental procedures. Cytochalasins A and B were dissolved in dimethyl sulphoxide (DMSO) and diluted in balanced salt solution to give a maximum final concentration of DMSO of 2.5% (v/v). Preliminary experiments revealed that DMSO at these concentrations had no effect on the release of histamine by Compound 48/80. Colchicine was dissolved in balanced salt solution. Cells were incubated with the specified concentrations of cytochalasins or colchicine for 20 min before exposure to Compound 48/80 at 0.2 µg/ml. After a further 10 min the reaction was stopped by centrifugation and aliquots of the supernatants and boiled cell debris were analysed for histamine release using a modified spectrofluorometric method⁹.

Male CRF/F rats (100 g) were sensitized by intradermal injection of rat anti-*N. brasiliensis* reaginic serum¹⁰. Twenty-four hours later pieces of subcutaneous connective tissue were removed from the sites of sensitization and maintained in Tyrode solution at room temperature until required. Tissues were incubated individually in 1.8 ml. of Tyrode solution at 37° C in a shaking water bath; usually groups consisted of five tissues, but in one experiment (experiment 2) of six tissues. Control groups were incubated in Tyrode, test groups were incubated for 60–90 min in cytochalasin B (10⁻⁵ M) in a 1% DMSO Tyrode solution. The challenge dose of antigen utilized per piece of tissue was 0.2 ml. of a 0.1 g% nitrogen preparation of *N. brasiliensis* antigen. Test groups were challenged after 30 and 60 (experiment 1) and 90 (experiment 2) min incubation either in Tyrode alone or in Tyrode and cytochalasin B. Ten minutes after antigen challenge, tissues were removed from the

medium, fixed in methanol, stained and the percentage of degranulated mast cells was determined.

The results in Table 1 show that cytochalasins A and B strongly inhibited the release of histamine from rat mast cells induced by Compound 48/80. By contrast, the inhibition by colchicine (Table 2) was slight, even at high concentrations (10^{-3} M). Similarly, cytochalasin B (10^{-5} M) strongly inhibited antigen-mediated histamine release from rat subcutaneous tissue (Table 3). Penetration was evidently slow. Inhibition was slight after 30 min incubation before antigen challenge, and greater after 90 min than 60 min preincubation. Experiments with cytochalasin A were unsuccessful because it came out of solution during the preincubation.

Table 1 Effect of Cytochalasin A and B on Compound 48/80-induced Release of Histamine from Rat Peritoneal Mast Cells

Treatment	% Histamine release	% Inhibition
—	2.2 ± 0.7	—
48/80*	53.0 ± 4.7	—
Cytochalasin A 5×10^{-5} M	2.2 ± 0.1	—
48/80 + Cytochalasin A 5×10^{-5} M	1.6 ± 0.7	100
48/80 + Cytochalasin A 1×10^{-6} M	1.6 ± 0.7	100
48/80 + Cytochalasin A 1×10^{-6} M	31.0 ± 5.2	41.5
Cytochalasin B 1×10^{-4} M	3.0 ± 0	—
48/80 + Cytochalasin B 1×10^{-4} M	32.8 ± 1.5	38.1
48/80 + Cytochalasin B 1×10^{-5} M	41.2 ± 6.4	22.3
48/80 + Cytochalasin B 1×10^{-6} M	40.1 ± 2.6	24.4

* Concentration of 48/80 = $0.2 \mu\text{g/ml}$.

Table 2 Effect of Colchicine on Compound 48/80-induced Release of Histamine from Rat Peritoneal Mast Cells

Treatment	% Histamine release	% Inhibition
—	3.3 ± 0.7	—
48/80	66.0 ± 0.7	—
48/80 + Colchicine 10^{-3}	56.9 ± 0.1	13.8
48/80 + Colchicine 10^{-4}	54.5 ± 0.8	17.4
48/80 + Colchicine 10^{-5}	59.9 ± 0.2	9.2

* Concentration of 48/80 = $0.2 \mu\text{g/ml}$.

In view of the selectivity of action of cytochalasins, these observations suggest that actomyosin-like contractile microfilaments play an important role in the exocytosis of histamine-containing granules from mast cells when a selective "trigger" such as cell-bound antibody and antigen or Compound 48/80 is used. Calcium ions are required for both antigen and 48/80-induced histamine release from these cells^{11,12}, and also for initiating the contraction of actomyosin systems, including those in smooth muscle^{13,14} and in the peripheral cytoplasm¹⁴. We therefore postulate that the mechanism by which release of amine-containing granules from mast cells is triggered selectively is the entry into the cell of calcium ions from the extracellular environment. We suggest that attachment of antigen to cell-bound antibody or the selective action of Compound 48/80 produces a conformational change in a plasma membrane constituent, which allows increased permeability to calcium ions. This has not yet been investigated in mast cells, but has been extensively documented in other cell types exposed to the appropriate mediators^{13,15}. Entry of calcium ions would induce contraction of microfilaments in the peripheral cytoplasm of the mast cell, and this would be followed by granule extrusion. Release of histamine from mast cells could therefore be inhibited at two stages in this process: either by paralysis of the contractile microfilaments, as produced by cytochalasins, or interference with the entry of calcium ions induced by antigen or by Compound 48/80.

The concentration of colchicine required to inhibit histamine release from mast cells is much greater than that which disperses microtubules. This raises the possibility that the drug may have

some other effect on mast cells, comparable with the anti-inflammatory effect which is apparently unrelated to the antimicrotubular (microtubular) activity¹⁶. Suggestions that microtubules are directly involved in release of histamine from mast cells¹⁷ and of granules from other cells¹⁸ must therefore be treated with reservation. Although microtubules may provide a framework which helps to support peripheral cytoplasmic structures and guide the movements of granules towards the plasma membrane, the motive power for granule extrusion appears to come from contractile microfilaments.

Table 3 Effect of Cytochalasin B on Degranulation of Rat Subcutaneous Tissue Mast Cells mediated by Reaginic Antibody and Antigen

Group	Experiment 1 % degranulation	% Inhibition of specific degranulation	Experiment 2 % degranulation	% Inhibition of specific degranulation
Unchallenged controls	5	—	11	—
Antigen challenged controls	59	—	66	—
Antigen challenge + cytochalasin	33*	48	28†	69

* $0.025 > P > 0.010$.

† $0.005 > P > 0.001$.

The mechanism by which contraction of microfilaments in the peripheral cytoplasm of mast cells results in discharge of granules is not yet clear. Our electron micrographs indicate that mast cell granules may normally be retained within invaginations of the plasma membrane; possibly contraction of microfilaments opens these and allows the granules to escape. Alternatively, the microfilament network may form a continuous "cage", preventing access of large secretory granules to the plasma membrane; when the filaments contract, spaces between them may allow the granules to move to the plasma membrane, fuse with it, and be released.

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Gain Control in the Retina and Retinal Dynamics

We have explored the nature of the automatic gain control in the cat retina, the process underlying rapid light adaptation which attenuates signals reaching retinal ganglion cells from photoreceptors¹.

Adult cats were anaesthetized with ether and thiamylal sodium during surgery and with urethane during the experiment, and were paralysed with gallamine triethiodide. Stimuli were focused on the retina of the fully atropinized eye with a contact lens containing a 4.0–4.8 mm diameter artificial pupil to give fairly sharp images². An innovation in these experiments was to glue the eyeball to a brass quarter-ring with 'Eastman 910' cement (suggested by R. Shlaer). Ganglion cell responses to square wave illumination were recorded from single fibres in the optic tract. Each nerve impulse triggered a standard narrow pulse which passed through an RC filter (10 ms time constant) and thence to an 'Enhancetron' signal averager the sweep of which was triggered by the onset of each illuminated phase of the square wave. Responses to sixty stimulus cycles were averaged to yield smoothed impulse rate as a function of time after stimulus onset. Averaged responses were obtained with 0.4 Hz square waves because Cleland and Enroth-Cugell¹ found that the shape of the averaged response to such a slow square wave was a good indicator whether the response was purely central or mixed with surround antagonism. We shall discuss here only pure central responses.

For every cell, threshold luminances for circular stimuli of 0.18° and 11° diameter centred on the receptive field were determined. Using these measurements we calculated the total summing area, A_r , of the central response mechanism of the ganglion cell (compare ref. 1). With zero background illumination, the 0.18° spot (0.4 Hz) was directed onto the receptive field midpoint and its luminance was adjusted to produce a small response. Peak response magnitude was measured as the difference between the impulse rate during the last portion of the off-phase of the stimulus cycle and the maximum of the on-response (or minimum for off-centre cells). Peak response magnitude was chosen to be in the linear range of operation of the ganglion cell, between 20–40 impulses s^{-1} . Background illumination was added until the size of the averaged response was reduced by the retinal gain control. Then we increased stimulus luminance to make the peak response magnitude the same as before. This was repeated for a series of background luminances.

The log of the gain (peak response/stimulus flux, in units of impulses/quantum) was plotted versus log effective background flux, that is the product of background retinal illumination and A_r , as in Fig. 1A. We shall describe first the principal features of this graph, then discuss shape of responses at different points on the curve. At low background levels the gain is constant; gain begins to decrease sharply at a transition point at which the background flux is 3×10^{-11} lumens, or 5×10^4 quanta/second (507 nm) incident on the cornea, on the average. At higher backgrounds the curve becomes a straight line on log-log coordinates with a slope of about 0.9 (compare ref. 3). We studied retinal responses at background luminances below 1 cd m^{-2} . Responses in this region were dominated by rods⁴.

Barlow and Levick⁵ emphasized the similarity in shape of averaged responses at different backgrounds. We are struck by the differences between the responses. Three averaged responses are shown in Fig. 1B: one from the flat portion, one from the transition point, and one from the sloping portion over which gain varies inversely with the 0.9 power of the background. The response from the flat part has no transient; at the transition point the response shows a small transient but still has a significant steady state component; on the sloping portion the response is almost all transient. At any one point on the curve, response shape is invariant over some range of stimulus flux. Off-centre cells also become more transient in their response when their

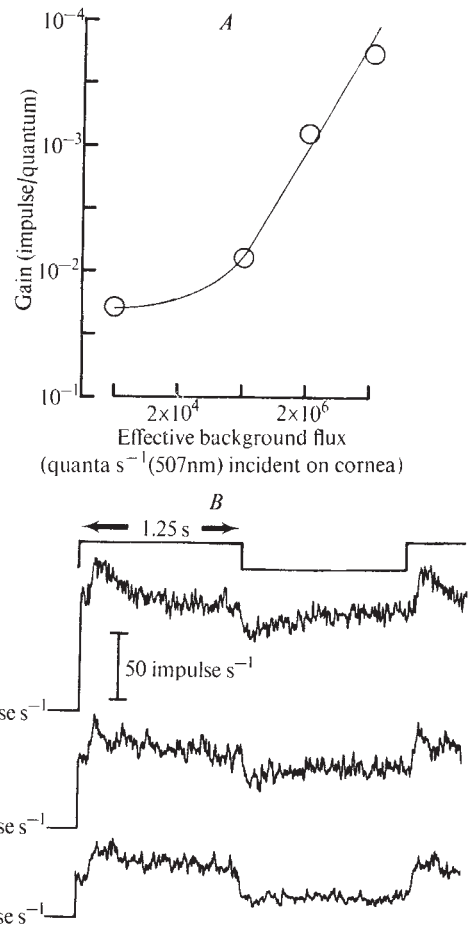


Fig. 1 A, Gain against background curve. Gain was calculated by dividing peak response (impulse s^{-1}) by absorbed quanta s^{-1} , on the assumption that 20% of quanta incident on cornea are absorbed. Effective background flux was calculated by multiplying total summing area of cell by background retinal illumination. Total summing area of this cell was 20 degrees². B, The three square wave responses are from the following backgrounds: bottom, 2×10^4 quanta s^{-1} (2×10^{-4} cat trolands illumination, equal to 10^2 quanta $deg^{-2} s^{-1}$, times 20 deg^2), middle, 2×10^5 quanta s^{-1} , and top, 2×10^6 quanta s^{-1} . Cell 20/3, on-centre.

gain is reduced by light adaptation. Sakmann and Creuzfeldt⁶ have displayed similar results.

It is important to note that response dynamics depend on gain setting, not on background retinal illumination. Background illumination is not the determinant of state of light adaptation of the central response mechanism; background flux (retinal illumination times area) is¹. To illustrate this point we show the experiment in Fig. 2, in which pure central responses were elicited by a small square wave-modulated spot superimposed on a concentric steady background of variable area. For each background area, stimulus luminance was set to evoke a response of approximately constant magnitude. As area of the adapting spot increased from A to C, gain decreased and the response became more transient. In this experiment, background illumination on the rods stimulated by the modulated stimulus remained constant. The change in gain and dynamics must have resulted from interaction.

The above results can be understood in terms of non-linear feedback from horizontal cells onto rods, a model for field adaptation we will present elsewhere. The idea of a non-linear feedback gain control is attractive because it links gain with dynamics. Feedback must occur after pooling of adaptive signals from many rods. Fig. 2, for example, is objective evidence for an adaptation pool. Furthermore, in many cells, background retinal illumination at the transition point provides 1 quantum per rod per 10 s; it is hard to believe individual rods are adapting in these conditions. Suggestive supporting

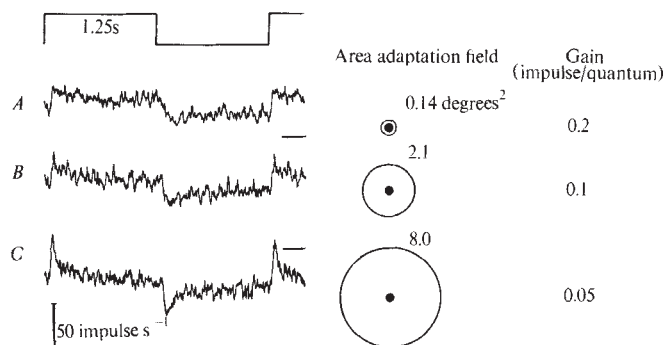


Fig. 2 Area and adaptation. Three averaged responses were elicited by a 0.18° diameter spot centrally located in the receptive field. Area of the concentric adapting disk was varied while its retinal illumination was constant at 10^{-2} trolands. Gain calculated as in Fig. 1. Stimulus in *A* was 0.33 trolands, in *B* 0.67 td, in *C* 2.6 td. Adapting flux in *B* brought this ganglion cell near to the transition point. Horizontal line under each response indicates 0 impulse s^{-1} . Total summing area of cell's centre was 7.5 degrees^2 . Cell 37/3, on-centre.

evidence comes from the work of Steinberg⁷ on cat S potentials, recorded in horizontal cells. He found a change in shape of response, from maintained to partially transient, "in partially light adapted retinae in response to flashes which mainly excited rods".

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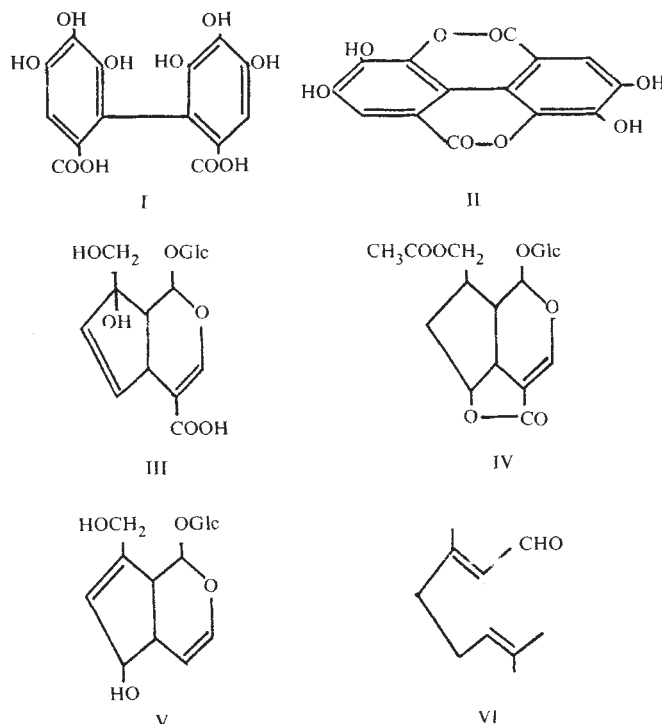
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Chemistry and Phylogeny of the Angiosperms

THERE are two classes of organic constituents of plants which seem to be confined to the dicotyledons: the ellagitannins (usually, if not exclusively, glucose esters of hexahydroxydiphenic acid); and a class of substances to which the name "iridoid" has unfortunately been given, of which asperuloside (IV) and aucubin (V) are the best-known members. Following Hegnauer's use of the term *aucubinartig* I propose to introduce the term "aucubinoid" for these substances. These compounds and the ellagitannins are distributed in an interesting way throughout the families and orders of the dicotyledons.

Ellagitannins are usually detected by the presence in acid hydrolysates of the tissues of ellagic acid, the dilactone (II) of hexahydroxydiphenic acid (I).

The occurrence of ellagic acid in the dicots was extensively reported by Bate-Smith². Its distribution is confined to a "cluster" of families broadly distinguishable as "Rosalian"³. It is absent from a second cluster similarly distinguishable as "Ranalian". The aucubinoids, reviewed by Hegnauer¹, also seem to be restricted in their distribution to the "Rosalian" cluster.



These, and other considerations of a chemical nature, have been incorporated in a summarized reclassification of the angiosperms⁴. A dendrogram in a recent publication by Takhtajan⁵ enables these suggested relationships to be seen very clearly. Takhtajan sees the angiosperms as deriving from magnolioid ancestors, with present-day branches represented in the dicots by the Magnoliidae, Hamamelidae and Dilleniidae. Associated with the Magnoliidae are the Caryophyllidae and Ranunculidae, and with the Dilleniidae the Rosidae and Asteridae (Figs. 1 and 2). The Magnoliidae association corresponds with the "Ranalian" and the Hamamelidae-Dilleniidae associations with the "Rosalian" cluster as conceived above.

In Figs. 1 and 2 the orders in which ellagic acid has been detected are printed in Roman type. A number of orders are missing from those recognized by Takhtajan because no records are available from them. The only orders in the Magnoliidae association in which ellagic acid has been found are the Plumbaginales and the Nymphaeales, attributions which may well be disputed. On the other hand, the more advanced orders of the Dilleniidae and Rosidae and the whole of the Asteridae are without ellagic acid, for reason which will be discussed later.

The distribution of the aucubinoids (Fig. 3) is both confirmatory of, and complementary to, that of ellagic acid, because, unlike the latter, they are not restricted to the more

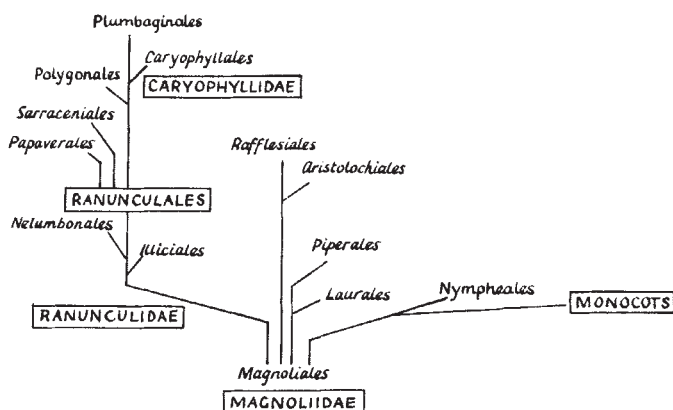


Fig. 1

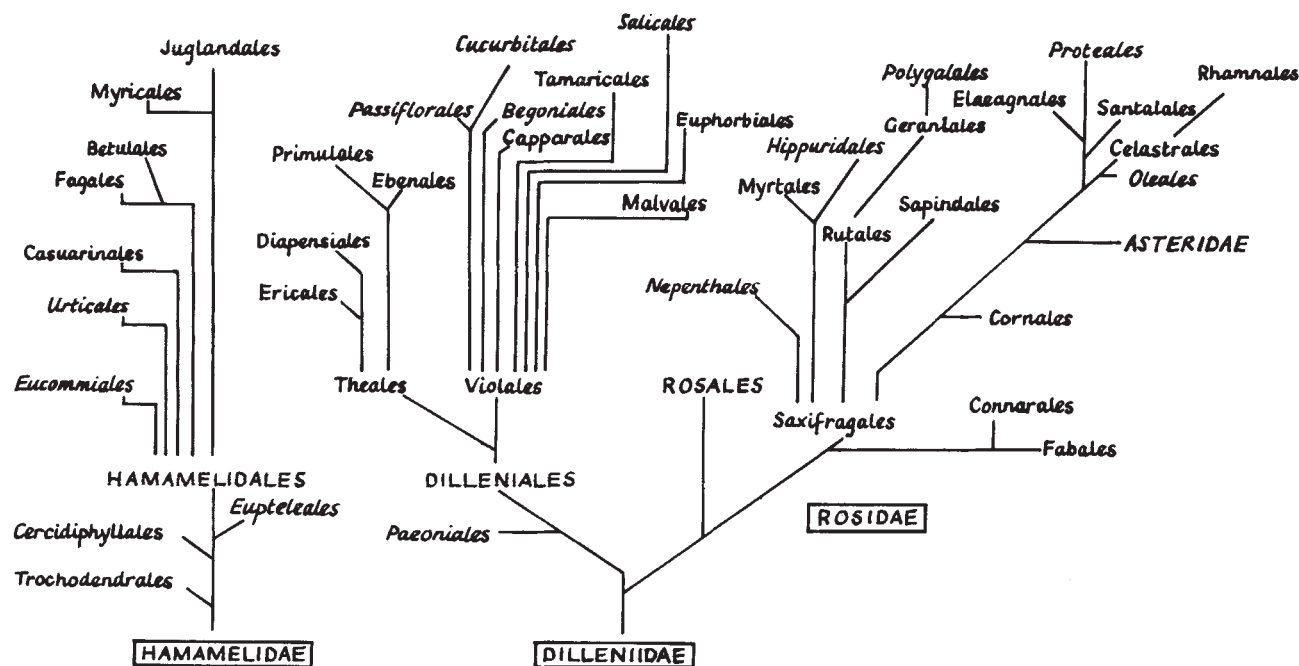


Fig. 2

woody families. The aucubinoids are, in fact, most richly represented in the mainly herbaceous orders of the (Englerian) Sympetaleae.

The critical question is when and where the ability to form these two classes of constituents arose in the course of angiosperm evolution. If the magnolioid is the single ancestral stock, the initiation of ellagitannin formation must have occurred within this stock later than the fixation of magnolioid characters. With this question is bound up the equally important one as to whether the ability to form ellagitannins—and also that of aucubinoids—has arisen once only, more than once, or even many times in the course of dicot evolution.

My present inclination is to start with the assumption that the magnolioid stock is ancestral to nothing but itself, and that the hamamelidoid–dillenioid (HD) stock is collateral with it from a point a long way back in the angiosperm record, but there is considerable uncertainty about familial or generic identifications earlier than the Upper Cretaceous^{5,6}. An authoritative discussion by J. Muller in ref. 6 of the palynological evidence gives the earliest identifications of living families or genera in the Senonian (70 m.y.). These and the identifications up to the Miocene (20 m.y.) are almost entirely in HD families. The first identification in the Magnoliales is of *Pseudowintera* in the Oligocene (40 m.y.), and the first in the

Magnoliaceae proper is at 20 m.y. All these dates are, of course, very far advanced from the first appearance of angiosperm pollen in the Lower Cretaceous (136 m.y., Banks)⁶. These records merely serve to show that the HD stock may be regarded as at least coeval with the magnolian.

Ellagitannins occur in the earliest of the genera in the record. *Liquidambar* is the first of the Hamamelidaceae, in the Palaeocene (60 m.y.), and this is also the first of the aucubinoid-containing genera. It seems likely that this is close to the origin of the aucubinoids, for monotropein (III), present in *Liquidambar*, is biogenetically one of the simplest members of the class. Asperuloside (IV) has a slightly more complicated structure and aucubin (V) has lost a carbon atom (a carboxyl group) from the original 10 carbon atoms of the citral skeleton (VI) from which Hegnauer³ regards them as being derived. Monotropein occurs also in the Ericaceae and the Pyrolaceae.

The further evolution of the two classes of compounds is as interesting as their probable origin. With increasing tendency to herbaceous habit, ellagitannins tend to die out, but the tendency is not so marked as in the case of the leucoanthocyanin tannins. The Geraniaceae, for example, are rich in ellagitannin although with very few exceptions herbaceous in habit. The aucubinoids, on the other hand, are more richly and frequently present in herbaceous plants such as the Scrophulariaceae, although they do appear first in the woody Hamamelidaceae and also in the Cornaceae and Rubiaceae. This contrasting behaviour may prove very valuable, because it is otherwise difficult to distinguish between those lines of plants which have once possessed ellagitannins and have lost them, and those which have never had them. Plants such as *Fouquieria*, *Cornus* and *Liquidambar*, which possess both, therefore occupy key positions in dicotyledonous phylogeny.

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¹ Hegnauer, R., *Pharm. Acta Helvet.*, **41**, 577 (1966).

² Bate-Smith, E. C., *J. Linn. Soc. (Botany)*, **58**, 95 (1962).

³ Bate-Smith, E. C., *Bull. Soc. Bot. France, Mem.* (1965).

⁴ Meeuse, A. J. D., *Acta Botan. Neerl.*, **19**, 133 (1970).

⁵ Takhtajan, A., *Flowering Plants: Origin and Dispersal* (Oliver and Boyd, Edinburgh, 1969).

⁶ Symposium on Major Evolutionary Events and the Geological Record of Plants, *Biol. Rev.*, **45**, No. 3 (1970).

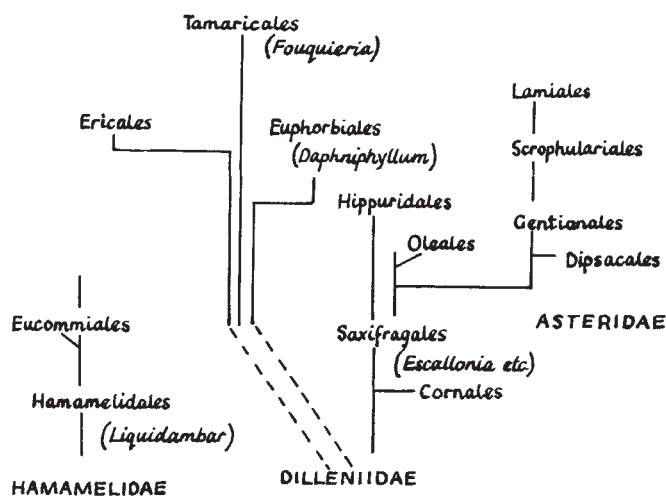


Fig. 3

BOOK REVIEWS

CBW in Perspective

The Problem of Chemical and Biological Warfare. (A Study of the Historical, Technical, Military, Legal and Political Aspects of CBW, and Possible Disarmament Measures.) Vol. 1: *The Rise of CB Weapons*. Pp. 395. Vol. 4: *CB Disarmament Negotiations 1920-1970*. Pp. 412. Vol. 5: *The Prevention of CBW*. Pp. 287. (SIPRI—Stockholm International Peace Research Institute.) (Almqvist and Wiksell: Stockholm; Humanities: New York; Paul Elek: London, November 1971.) Vols. 1 and 4: Sw.kr. 75; \$16.50; £7.50. Vol. 5: Sw.kr. 40; \$9; £4.

VOLUME 1 of this study traces the development of chemical and biological weapons (CBW) and their associated delivery systems from 1914, when chemists experimenting with toxic materials were killed in their laboratories, through to the discovery of nerve gases in 1945. One constant theme of this unedifying and sometimes macabre story is the struggle for advantage between offensive (in the strategic sense) and defensive capabilities. In the First World War, for instance, the filter in the army issue respirators had to be impregnated with an increasing number of different sorbents to protect the troops from an ever-growing range of gases.

Another theme is the propagandist use of allegations that the enemy of the moment has used chemical or biological weapons, to capitalize on popular fear and outrage. An appendix lists forty such allegations. Very few have been well established, and all those since 1918 have been in "downhill" conflicts, where the attacker had no reason to fear retaliation in kind.

Volume 4 is concerned with CB disarmament negotiations and proposals from 1920 to 1970. There have always been some who have rejected the whole notion of CB disarmament, on grounds of national security or the supposedly prophylactic effect of the weapons' existence. Then, again, the Norwegian delegate to a League of Nations committee in 1922 spoke for an important tradition in anti-war thought when he declared that "man was incapable of humanizing war and could only endeavour to abolish it". On the other hand, many people have welcomed the restraints of customary and treaty law, landmarks in which have been the Geneva Protocol of 1925, to which nearly one hundred states are now

party, and the Biological Weapons Convention recently completed and soon to be open for signature and ratification.

Volume 5, on the prevention of CBW, is the one most densely packed with argument. It begins with the restraints already accepted as law, and identifies those points at which the restraints are under most pressure. One area of weakness is the ill-defined border between civil hostilities, to which the laws of war still apply, and police actions, which lie beyond their reach. A second is the refusal of the American and Australian governments, and since 1970 the British (although here the matter is under review), to accept any longer that the existing restraints apply to all harassing as well as casualty agents. A third is the uncertain legal status of defoliants.

The SIPRI team comes down in favour of maintaining a comprehensive ban, but not before paying serious attention to the arguments of the would-be revisionists. The same generosity is accorded to the often spurious arguments that certain CB weapons are "humane". These two closely related controversies have seldom been as fully set out and argued as they are here, and the well-supported conclusion is reached that "humaneness" is a property not of a weapon but of the military context in which it is used. This may not be susceptible to accurate prediction, for it "will depend not only on the weapon, but also on the intention of the user and the extent to which intentions are translated into practice".

The authors can hardly disguise their disappointment at the Soviet *volte-face* in March 1971 which has made possible the conclusion of a multi-lateral treaty providing for biological but not (except for toxins) chemical disarmament. They remain unconvinced by the strong arguments, associated particularly with British diplomacy, for negotiating on biological weapons first. A handy table of possible treaty contents shows clearly where the choices have to be made in the negotiation of successive instruments which, it is hoped, will supplement rather than detract from the Geneva Protocol. Also included is a most useful section on verification, noting particularly the safeguards already operating internationally in Western Europe and the attractions of a complaints procedure as a substitute for a permanent

inspection system. Most welcome of all, included in the excellent documentation, is a resolution of the Tenth International Congress for Microbiology, 1970, specifying twelve ways in which military facilities could be converted to peaceful applications of microbiology.

One outstanding quality of the study is its treatment of the vexed question: what is the function of legal restraints on conduct in war? They are seen as reinforcements in a delicate balance of pressures and inhibitions out of which—and not from moral, or legal, or prudential considerations alone—decisions are reached to use or not to use particular weapons. The fact that the belligerents in the Second World War refrained from unleashing their fast-developing chemical weapons has often been attributed, uncritically, to the existence of the Geneva Protocol; or, equally uncritically, to the deterrent effect of the knowledge that the other side could retaliate. The SIPRI team's careful analysis of the constraints operating on the principal governments in this case, and in general, is just the kind of reasoning that the systematic study of disarmament and arms limitation requires. A range of explanatory concepts is developed, notably "acceptance", which will undoubtedly help future theorists in this area.

The publication of these three volumes partially out of sequence means that there are bound to be some tantalizingly loose ends strewn around. How will volume 3, on the international law of CBW, prove the extensive interpretation of the Geneva Protocol, as covering all gases including irritants, to be the correct one? Will it produce any new evidence from the *travaux préparatoires* of 1925 to challenge the Wilson Cabinet's disastrously misguided preference for a restrictive interpretation excluding "CS and other such gases"?

Some readers may be mildly impatient with the length of each volume, but the only unnecessary repetition is the catalogue of alleged uses of CBW in twentieth century conflicts. They are listed in full as an appendix to volume 1, revisited selectively for their relevance to verification problems in volume 4, and turn up yet again in volume 5.

A minor criticism of a major enterprise. The careful research and years of checking and consultation that are reflected in it, the cogency of argument,

the elaborate documentation, and not least the high standard of production (from the presses of Almqvist and Wiksell), make this a study to be welcomed and one that will be of lasting value.

NICHOLAS A. SIMS

Functional Neurology

Functions of the Nervous System. By Marcel Monnier. Vol. 1: *General Physiology; Automatic Functions (Neurohormonal Regulations)*. Pp. xxiv+671. £18. Vol. 2: *Motor and Psychomotor Functions*. Pp. xviii+658. £20. (Elsevier: Amsterdam, London and New York.)

THESE two volumes are the first of four, volumes 3 and 4 to deal with sensory functions and psychic functions respectively.

The expressed intention of the first volume is to integrate the physiology of the visceral autonomic system with the somatic. The volume is divided into three parts, the first being the general physiology of the nervous system, a concise but well written account of electrophysiological methods and functions of neurone, nerve fibre and synapse.

The second part deals with the organization of visceral functions and this section is one of the most interesting and important in the volume, the central organization being particularly fully covered. It is noticeable throughout that the author, like his teacher Hess, postulates functional centres demonstrated by electrical stimulation. Many workers, however, would prefer the term "pathway" to "centre", for the same effects could be produced by stimulation of either a centre or a pathway. Unfortunately it has not been possible to include some of the most recent and important studies of the late sixties, particularly of hypothalamic vasopressor and vesicopressor pathways, and the autonomic pathways in the cord receive very little attention.

Volume 2 continues the integration of autonomic and somatic function. The first part is the general organization of motor functions and the second part is devoted to special motor functions and to the concept of the functional organization of motor factors in the central nervous system. The author has used a functional plan based on defensive functions, postural functions, equilibration, righting, and stabilization of the extremities rather than an anatomical classification, hoping in this way to show how elementary mechanisms are integrated at successive levels. At the end of each chapter is a valuable summary. Throughout the volume the illustrations are of high quality, although Figs. 136, 137 and 177 appear to be of a different style and lower standard. The psycho-

motor content of the volume presumably refers to chapters 27 and 28 relating to speech.

The whole book is an excellent reference work with exhaustive bibliography and good illustrations. The clear presentations are of particular value to clinicians—there are, for example, more than 140 references to different reflexes.

This is certainly not a book for light reading and whatever one's views about the shortcomings of any particular section the whole work is a most formidable undertaking and the author's intention to produce an integrated work has on the whole been successful. Undoubtedly this is one of the most important books on the nervous system to be produced in recent years and is an essential addition to every medical library whilst doubtless many individual volumes, despite the high price, will find their way to investigators' bookshelves. EDWARD HITCHCOCK

Advanced Reactor Theory

Nuclear Reactor Theory. By George I. Bell and Samuel Glasstone. Pp. xviii+619. (Van Nostrand Reinhold: New York and London, February 1971.) £12.25.

IN the nuclear reactor field the name of Glasstone is invariably linked with textbooks of international repute. In this volume the collaboration of such authorities as Dr Bell and Samuel Glasstone, both of the University of California, has produced what is surely destined to become a standard reference on reactor theory at an advanced level.

This is not a book for the newcomer to the reactor field. Rather, it is a worthy extension of Glasstone and Edlund's *Elements of Nuclear Reactor Theory* and the student would be well advised to master the contents of that book before embarking on Bell and Glasstone's new book. This means that he should have a thorough understanding of the physical processes occurring within the reactor core. There should be familiarity with the processes of fission, neutron scattering and absorption, resonances, criticality and burn-up problems and some knowledge of conditions which promote instability. A sound mathematical background is essential.

To a teaching physicist the first half of the book appears mainly mathematical, the remainder has a more physical approach. Thus, the book starts with the derivation of the neutron transport equation and subsequent chapters consider its solution in various geometries and by different mathematical methods. Solutions for single and multigroup neutrons are evolved and the accuracies of these are com-

pared. These bare statements précis a very full treatment which lasts over some 200 pages and includes many aspects of neutron flux distributions too numerous to list here. Two more chapters on discrete ordinates and perturbation theory make up what may be regarded as a mathematical preparation for the second half of the book. The longest chapters deal with neutron thermalization and resonance absorption. With sections on coherent and incoherent scattering, "cold" neutron effects, and with the consideration given to time dependent sources, neutron thermalization can be judged to have adequate discussion. As might be expected, the resonance absorption chapter concentrates on Doppler broadening, the objective being to derive the absorption and group constants for both homogeneous and heterogeneous media. The remaining two chapters are typical of the thoroughness of treatment throughout the book; some 130 pages are given to reactor dynamics covering both time dependent and space dependent conditions. The time dependent point reactor model kinetic equations are extended for both zero and power levels. There is a valuable section on reactor transfer functions and their application with reactivity perturbations to determine core characteristics in respect of prompt and delayed neutrons and the stability of the reactor system. The tenth and final chapter considers space dependent neutron transport problems and the instabilities likely to occur through xenon concentration changes and fuel burn-up. There is no chapter specifically for the problems of fast reactors though these are mentioned in three chapters. A surprising omission is any reference to neutron flux enhancement by fast fission. Finally, an appendix deals very clearly with the various mathematical functions used in the text, a section of value to those whose mathematics is rusty.

Apart from its content, the structure of the text approaches the ideal. An introduction to each chapter sets out precisely the work it aims to cover and the methods to be adopted. In the early chapters, for instance, several methods of solving the neutron transport equation are given and the accuracies of the methods compared. Equations are derived more by argument than by rigorous mathematics. The manipulation of these equations is adequately explained even for the less mathematical reader and almost always there is a physical explanation of the final mathematical statement. Apart from a very few lapses, symbols are defined as they are introduced. This is correct, but the absence of a list of symbols does mean that if the book is used as a reference there is much searching of earlier pages to identify the symbols. Each chapter

has its set of exercises—about 100 in total—in some of which a good reactor background knowledge is assumed. Most of the exercises require the derivation of a mathematical function or equation similar to that in the text. A few exercises are numerical but no answers are given; they are to be checked by comparison with values quoted in the text or in references.

The text excels in cross referencing both forward and backward. Fortunately this is done unobtrusively and does not distract the reader's attention. External references are extensive, ranging up to 100 references in several chapters and up to 1970 in date. These references taken in conjunction with the *Science Citation Index* should ensure a competent survey of the reactor literature well into the future.

The book is obviously destined as a reference work but its place is likely to be in libraries or on the shelves of reactor designers and academics. It is undoubtedly a sound investment for specialists.

R. R. OSBORNE

Water Balance

Endocrines and Osmoregulation: A Comparative Account of the Regulation of Water and Salt in Vertebrates. By P. J. Bentley. Pp. xvi+300. (Springer: Berlin and New York, 1971.) 58 DM; \$16.80.

VERTEBRATES occupy a very wide range of ecological niches, ranging from sea and fresh water to arid deserts. For the most part, homeostatic mechanisms are brought into play to limit variations in the constitution of the body, in which water and electrolyte composition is of great importance. Here there are two important areas, the relationship of the whole animal to the particular environment and the maintenance of the different compartments of the body, so that, as a simple example, a solution largely composed of sodium chloride bathes cells with high potassium content. Investigation of such problems requires concepts of physico-chemistry and biochemistry and for which the first fourteen pages of chapter 1 present a brief introduction. The biological structures which take part in exchanges of water and electrolytes, such as cell membranes, capillaries, skin, gills, gut, urinary bladder and kidneys, are then discussed. The first chapter thus gives the background to the main purpose of the book, that is to show how the endocrine system impinges on these basic facets of regulation throughout the vertebrates. Chapter 2, the vertebrate endocrine system, starts off with a page and a half on servo-control systems and, in smaller print, gives the criteria of endocrine function, the methods used and the

difficulties encountered. This is a short but important section of the book and should either have been cast in the general format or added as an appendix. Each gland is then taken in turn and constitutes a summary of comparative endocrinology, with emphasis on mechanisms concerned with water and electrolyte movements. Although much has to be repeated in the following five chapters, it does provide an introduction to endocrine organs and gives the background for wider reading by younger workers to whom the book is primarily devoted.

The main contribution of the book lies in the survey of the vertebrate classes, starting with the mammals and ending with the fishes, both agnathous and gnathostomatous. These chapters are particularly well done and the coverage of the literature is excellent. It is especially pleasing to find the Australian fauna given their full due. Whilst some might rejoice in the great research application to sheep, a real consumer concept, the comparative endocrinologist also hopes for more investigation of the rich variety of animals peculiar to that continent. With the vertebrate endocrine glands, particularly posterior lobe and adrenocortical hormones, the author comes into his own. His authoritative survey, including discussions on the animal's physiology in relation to the environment, is well documented and supported by good tables and figures. I strongly recommend it as an essential reading and reference book for younger and older workers alike.

I. CHESTER JONES

Medical Policy

Medicine and Society: Contemporary Medical Problems in Historical Perspective. (Four Symposia.) Pp. viii+378. (American Philosophical Society: Philadelphia, 1971.) \$2.50.

THE collection of any group of papers as a book always presents hazards, and this photo-offset typescript of four symposia conducted by the Departments of the History and Sociology of Science of Bryn Mawr College and the University of Pennsylvania is no exception. Organized under four headings, "Human Experimentation," "Drug Addiction and Control," "The Twentieth Century Hospital," and "Alternative Traditions of Medical Care," fourteen lectures and the discussions which followed have been published without benefit of editing. The virtue of informal presentation must have been compelling at the time of these meetings; unfortunately this does not lead to a coherent volume. A cross-disciplinary approach requires more rigorous control of material than these circumstances elicited, and the

verbatim transcription of the discussions suggests the need for a more confining focus in the absence of a common methodological framework. Undoubtedly these symposia were enormously stimulating for all participants, but they do not make especially illuminating reading.

The formal participants included historians, sociologists, physicians from several specialized fields, a lawyer and a hospital administrator; men and women whose published works command respect and provide the resources we turn to for guidance in interpreting the data of past and present medical events. To name Renée Fox, Robert S. Morison, David F. Musto, Charles Rosenberg, Anne R. Somers, Jeanne Brand and Mark G. Field gives some indication of the breadth of scholarship encompassed. These symposia were not, however, the time for presenting new research, nor the occasion for rewarding syntheses. The panel on "Drug Addiction and Control" seemed the most successful exchange, for Dr Musto's contribution provided both data and analysis which induced comparative examination. The final session on "Alternative Traditions of Medical Care" seems, for quite different reasons—perhaps in part because the student participants became accustomed to the opportunities and constraints of this type of discussion—to have evoked the sharpest confrontations. Unfortunately this seems also to have resulted in more heat than light.

Historians of medicine will welcome this pioneering attempt to engage experts from diverse fields and students of several disciplines in an exchange of information and ideas. From this kind of interaction new and more fruitful methods of historical and contemporary analysis should eventually emerge. At the moment one must conclude, however sadly, that the papers published here resemble sturdy ocean-going vessels passing each other by on the high seas, and too often this encounter takes place in the dark.

BARBARA G. ROSENKRANTZ

Mosquitoes in General

Mosquitoes. By J. D. Gillett. Pp. xiii+274. (Weidenfeld and Nicolson: London, November 1971.) £5.90.

THE significance of mosquitoes as vectors of disease was demonstrated during the later years of the nineteenth century, and for the past seventy years mosquitoes have been subjected to intensive study. They comprise some 2,500 species in thirty-three genera, and many species have been implicated as vectors of human disease, transmitting viruses, protozoa or nematodes. Laboratory studies have been concentrated on

a few species, notably *Aedes aegypti*, *Culex pipiens*, and one or two species of *Anopheles*, but field workers have studied a large number of vector and suspected vector species in many parts of the world.

Professor J. D. Gillett spent more than twenty years in Africa working both at the bench and in the field on the biology of important vector species. When he started this work the foundations of the subject had been laid and research was developing at advanced levels. His own research encompassed studies of disease transmission, egg diapause, ovarian development and, perhaps most notably, of the role of circadian rhythms in mosquito behaviour. Professor Gillett has now written an account of mosquito biology for the general reader. The reader soon becomes aware of the wide variety of behaviour patterns displayed by a family of structurally similar insects, and of how a knowledge of these behaviour patterns is essential if one is to understand the biology of any species and its interactions with other organisms. The author also emphasizes that mosquito species are composed of partially isolated and largely non-interbreeding populations which can differ greatly in their relationships with man or other vertebrate hosts.

Professor Gillett takes us through the life cycle of mosquitoes, describing the biology of the different stages and often illuminating the text with observations from his own experience. The section on host-seeking is disappointing and some chapters would have been much clearer if they had contained line drawings, but as a whole the book contains an informative and very readable account of the complex and interesting lives of these beautiful and dangerous insects. In the final chapters the author describes the epidemiology of the principal human diseases transmitted by mosquitoes, giving emphasis to yellow fever and to some recently discovered viral diseases. The reader who has some knowledge of biology will gain from this book an understanding of the biology of an important family of insects of which we have remarkably extensive if still incomplete knowledge.

A. N. CLEMENTS

Senses of Fish

Fish Physiology. Edited by W. S. Hoar and D. J. Randall. Vol. 5. Pp. xvi+600. (Academic: New York and London, October 1971.) \$32; £14.95.

THIS handsomely produced book is a worthy extension of the multi-volume treatise which aims to cover all aspects of fish physiology in considerable detail. As the editors say in the preface: "The chapters in this volume, perhaps more

than in other volumes, can only present a summary of the present state of science in this rapidly expanding and developing field." With this statement one would generally agree, though, as in most collaborative efforts of this kind, the contributors display in varying degree the art of abstracting concisely essential points from original research. The number of pages allotted to each topic can, therefore, give only a superficial indication of the state and progress in any one field. The galaxy of experts who contributed is a guarantee of high standards, although some chapters, for example, that on temperature receptors, seem mainly of value in emphasizing the paucity of available information and the need for further work. One can hold different views on the composition, balance and arrangement in this volume. The excellent article on the Mauthner cell might have been better placed in the previous volume in context with the central nervous system. Some apologies are made for inclusion of a very detailed chapter on electric organs, justified by its bearing on electroreception. The derivation of electric organs from neuromuscular elements prompts one to search in vain in present or future volumes for an article dealing with the motor system in fish. This seems a strange omission, for the main bulk of a fish is muscle, which, quite apart from its academic interest, is of great importance to non-specialist members of the human race. In the end, however, each chapter in this as in the other volumes stands in its own right, only loosely linked to the rest. The scholarly treatment and the inclusion in some chapters of material not previously published are welcome; this contrasts with others which have been reviewed by the same authors with alarming regularity in recent years—in annual reviews, in handbooks of comparative or sensory physiology, in symposia volumes, progress reports and so on. The flood of advertising leaflets arriving daily on one's desk bears witness that the reviewing epidemic shows no signs of abating. This places a prospective buyer of *Fish Physiology* in a dilemma and provokes some unholy thoughts: he may only want the new bits and is made to pay for the lot. If only some of the advertising money could be deflected into research instead of re-hash! Reviewers of earlier volumes of *Fish Physiology* have grumbled about the high price (£8 8s in 1969); the cost of the 1971 volume is £14.95. The avowed aim of the work is to serve fisheries research laboratories and university reference libraries, and no library which has invested in earlier volumes would wish to break their series. It is fascinating to speculate about the complex web of drives from

which springs the publication of such works. It may be the noble wish to minister to the needs of the scientific community; it may be an expression of the business acumen of publishers, combined with the inability of some authors to say "No" when advances are made to them. Certainly a more rational use than we see at present of financial resources available for dissemination of scientific information is conceivable. This is not to say that volume 5 of *Fish Physiology* is not a useful book to have on one's shelf. It is a landmark in the jungle of proliferating scientific literature.

H. W. LISSMANN

Sugar

Sugar: Chemical, Biological and Nutritional Aspects of Sucrose. By John Yudkin, Jack Edelman and Leslie Hough. Pp. 246. (Butterworth: London, June 1971.) £4.50.

IN 1969 the departmental heads of Chemistry, Nutrition and Botany at Queen Elizabeth College, London, combined to organize a symposium on sugar (sucrose). This was long overdue in view of the fact that sucrose is the principal pure chemical in our diet, and it is appropriate that this multidisciplinary symposium should be held at a centre of such high international repute in the field of carbohydrates. This book, which represents the proceedings of the symposium, is the fullest and most up-to-date collection of scientific opinion on the chemistry and biology of sucrose.

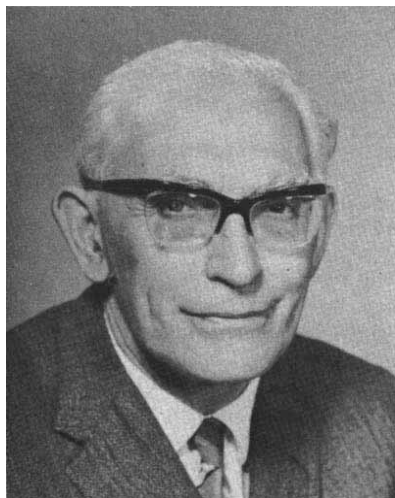
The current focus of international opinion on sucrose is due, in large measure, to its effects on mammalian organisms. Many workers allege that the disaccharide may be a contributor to ischaemic heart disease, dental caries, gastrointestinal disorders and many other illnesses. Most of these suggestions, however, are still open to question and indeed doubt, for the replacement of dietary sucrose with other sweeteners may be an even more hazardous undertaking. No medical or physiological advances in our understanding of sugar metabolism can succeed without parallel advances at the molecular level, and although sucrose is structurally well understood the reasons for the biosynthesis of such an asymmetric substance are still obscure. Thus botanically and zoologically the origins and subsequent metabolic fate of the sucrose molecule are under investigation throughout the world.

All scientists, industrialists and medical personnel interested in the uses, effects and future potential of sugar should find this book to be of great value. It is concise and thorough and supported by an excellent bibliography.

G. G. BIRCH

Obituary

Dr Norman Allen



NORMAN PERCY ALLEN, CB, FRS, died on February 23, 1972, at his home in Weybridge. From 1944 until 1967 he was Superintendent of the Metallurgy Division of the National Physical Laboratory, and in 1966, when the Materials Group was formed at the National Physical Laboratory, he was made the first head of the group and appointed Deputy Director. He retired from the post of Deputy Director at the end of 1967.

Allen was born in 1903 in Wrexham, Denbighshire, and graduated in metallurgy at the University of Sheffield, obtaining the M.Met in 1924. He spent the following five years at University College, Swansea, in the company of a number of others who have subsequently become famous in the metallurgical world. He worked there for the British Non-Ferrous Metals Research Association and afterwards at the University of Birmingham, where he became a senior lecturer and made important studies of gaseous in metals, particularly the causes of porosity in copper and silver ingots. For this work he was awarded the DSc degree in 1934.

In 1935 Allen went to the Mond Nickel Co where he was senior research metallurgist, engaged on a variety of work, which in later years took place during the war and hence was not published. Two important advances during this period were made. The first was the understanding of transformations in alloy steels and their influence on the mechanical properties of the product. The differences between low alloy and plain carbon steels were revealed by measurements of transformation velocities, and following this, the design of

steels in terms of their hardenability became possible. The other achievement was the development of the first nimonic creep-resisting alloys which were used in the hottest parts of the first jet engine.

Allen joined the NPL in 1944, when he was appointed Superintendent of the Metallurgy Division in succession to Dr Sykes (now Sir Charles Sykes). During his superintendency many important advances in alloy design and in the utilization of new metals took place. The division made considerable contributions on the metallography of uranium and the preparation of beryllium, before the AEA work at Harwell got started, and the deformation and fracture of iron and its alloys. The application of electron microscopy to the study of metals also took place under Allen and his interest in electron microscopy continued until his death. He was particularly instrumental in starting the work on measurement of surface and grain boundary energies, because he believed that the grain boundary energy was a controlling parameter for the work of fracture of high strength steels. He also started important work on the soft X-ray spectroscopy of metals and the mechanical properties of alloys at elevated temperatures, including the creep of steam turbine materials, the thermal fatigue of gas turbine alloys, the thermodynamics of alloys and the metallurgy of titanium.

Allen had a keen insight into materials and was instrumental in setting up the Materials Group at NPL, which included the work not only on metals but also that on inorganic materials, plastics and on the physical properties of a number of chemical substances.

His interest in the development of steel remained, however, and during his period at NPL work was carried out which demonstrated the high toughness and high yield strength which could be obtained by lowering the carbon content of normal mild steel. This work, and the emphasis on the importance of increased quantities of manganese were instrumental in BISRA's subsequent success in patenting, throughout the world, special processes for the controlled rolling of mild steel.

For his work on alloy steels and the development of their engineering properties Allen was elected to the Royal Society in 1956. In 1962 he recognized the potential importance of the development in the United States of high field

superconductors based on the niobium-tin system and was instrumental in setting up in Britain a collaborative project, sponsored by the government, which operated for a number of years and made possible the production of superconducting materials. The management of the Superconductivity Project was carried out under his direction and it coordinated the efforts of industry, universities and government. As a member of many government committees concerned with the application of metallurgy in defence and the nationalized industries, Allen exerted a very considerable influence over the development of materials in this country throughout the fifties and early sixties.

In 1961 Allen was President of the Institution of Metallurgists and was awarded the CB in 1966. He was awarded the Osmond Medal of the French Society of Metallurgy and many honorary degrees from universities in Britain and abroad. He received the Bessemer Gold Medal of the Iron and Steel Institute in 1965 and the Platinum Medal of the Institute of Metals in 1967. He was also honoured by the Italian Association of Metallurgy, and achieved the rare distinction in the last year of his life of being elected a Fellow of the Institute of Metals.

Allen was always a man of definitely held views, and metallurgists and colleagues throughout Britain, as well as in America and Europe, will miss his whole-hearted method of assertion and his generous enjoyment of a thoroughly good scientific argument.

Professor Peter Preiswerk

PROFESSOR PETER PREISWERK died on January 28, 1972, a few days before his retirement at the age of 65 from the European Organization for Nuclear Research (CERN) at Meyrin, near Geneva.

Preiswerk was born at Basle, Switzerland, in 1907. As a student he attended Basle University and later the University of Berlin where his teachers included many of the great physicists of that time: Nernst, Planck, von Laue, Schrödinger and Bothe. He was awarded his doctorate in 1933, after his return to Basle University.

In 1934 he joined the laboratory of Madame Curie in Paris and became a collaborator of Frédéric and Irène Joliot who had just announced their discoveries in artificial radioactivity. Later he worked on slow neutron physics with

H. V. Halban and among the many papers they published was one reporting that neutrons reached thermal equilibrium in hydrogenous substances and another that the resonant absorption of neutrons is dependent on their velocity. This slow neutron research later became of great importance in the field of nuclear power development.

At the end of 1936 Preiswerk returned to Switzerland and became involved in building a cyclotron at the Eidgenössische Technische Hochschule (ETH) at Zürich and later on he published many papers on nuclear spectroscopy. He lectured on experimental physics from 1964 onwards and became a professor at the ETH in 1950.

In December 1950 he was present at a meeting of the Commission of Scientific Cooperation of the European Cultural Centre where the idea of creating a European high energy physics laboratory was discussed. This event proved a turning point in his career and he devoted the rest of his life to the realization of this European scientific venture. One of the early problems was to find a site for the new European laboratory and, at the December 1950 meeting of the Commission, Preiswerk suggested two possible sites—one near Geneva, which he preferred, and the other in Alsace near Basle. After much discussion, the Geneva site was finally chosen amongst many proposed by different countries, and hence the establishment of what later on became the European Organization for Nuclear Research (CERN) at Meyrin near Geneva was due to his initiative.

In addition to suggesting a site for the new laboratory, Preiswerk played an important role in bringing the laboratory into existence. He was one of the experts who were called together by Professor Auger in 1951 to co-ordinate the wishes of the European scientists and to determine the aims and

nature of the organization. When an interim organization was set up, Preiswerk became the deputy leader of the laboratory group whose task it was to plan the new laboratory, and a member of the executive group, which directed the overall planning. In 1954 he became Director of the Site and Building Division of CERN and hence responsible for the design and construction of the buildings and installations on the Meyrin site. When the initial construction period was over in 1958 he joined the Synchro-cyclotron Division and in 1961 he became the leader of the Nuclear Physics Division, a post which he held until 1971.

Thus from 1950 to the end of his life, a period of over 20 years, Preiswerk was intimately and often passionately involved in the creation and operation of the CERN Laboratory near Geneva. The success of CERN is in no small measure due to his untiring devotion. When, in 1971, after many vicissitudes, it was finally decided to build the new European 300 GeV accelerator, eleven times the size of the first "giant" machine, next door to the existing CERN Laboratory, nobody was more delighted than Preiswerk.

The European scientific interests of Preiswerk were not only confined to the CERN Laboratories. He also played a leading role in setting up the European Physical Society a few years ago and was the chairman of its High Energy and Particle Physics Division.

Professor Peter Preiswerk will be remembered not only for his research work but also for his outstanding contribution to the idea of European collaboration in scientific research and to its realization in the field of nuclear particle physics. He will be remembered with gratitude by all the thousands of European nuclear physicists who use, now and in the future, the experimental facilities which he did so much to create.

Announcements

University News

Dr Keith R. Jennings, University of Sheffield, has been appointed first professor of physical chemistry in the University of Warwick.

The title of professor emeritus has been conferred on **Professor Norman C. Sidwell** who retired in December 1971 from the post of professor and head of the Department of Building in Heriot-Watt University.

Dr Edgar Stones, University of Birmingham, has been appointed to the William Rosco chair of education in the University of Liverpool; the status and title of professor in the Department of Oceanography has been conferred on **Dr J. P. Riley**; and **Dr J. L. Alty**, International Business Machines (UK) Limited, has been appointed director of the Computer Laboratory.

Appointments

Professor H. N. Robson, vice-chancellor of the University of Sheffield, has been elected chairman of the Committee of Vice-Chancellors and Principals of the Universities of the United Kingdom, in succession to Sir Fraser Noble, vice-chancellor of the University of Leicester.

Professor Norman C. Sidwell, Heriot-Watt University, has been reappointed chairman of the Scottish Committee of the National House-Builders Registration Council.

Professor G. Puppi has been re-elected president of the Council of the European Space Research Organization; **Mr J. van Eesbeck** has been re-elected and **General L. de Azcarraga** elected vice-presidents of the Council.

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